EXHIBIT 16

8234739

THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 25, 2022

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APPLICATION NUMBER: ***16/112,453***
FILING DATE: ***August 24, 2018***
PATENT NUMBER: ***10,266,827***
ISSUE DATE: ***April 23, 2019***

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

W. Montgomery
Wanda Montgomery
Certifying Officer

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 16112453

Document Date: 08/24/2018

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- Sequence Listing

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Form Revision Date: August 26, 2013

PTO/AIA/15 (10-17)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	4140.01500B1
First Named Inventor	Stephen Donald WILTON
Title	See attached addendum
Priority Mail Express® Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**

1. ☐ **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. ☑ **Applicant asserts small entity status.** See 37 CFR 1.27
3. ☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. ☑ **Specification** [*Total Pages* 68]
   Both the claims and abstract must start on a new page.
   (See MPEP § 608.01(a) for information on the preferred arrangement)
5. ☑ **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 22]
6. **Inventor's Oath or Declaration** [*Total Pages* ____]
   (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))
   a. ☐ Newly executed (original or copy)
   b. ☐ A copy from a prior application (37 CFR 1.63(d))
7. ☑ **Application Data Sheet** ** See note below.*
   See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R**
   in duplicate, large table, or Computer Program (*Appendix*)
   ☐ Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission**
   (if applicable, items a. – c. are required)
   a. ☑ Computer Readable Form (CRF)
   b. ☐ Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statements verifying identity of above copies

ACCOMPANYING APPLICATION PAPERS

10. ☐ **Assignment Papers** (cover sheet & document(s))
    Name of Assignee ____
11. ☐ **37 CFR 3.73(c) Statement** *(when there is an assignee)* ☐ **Power of Attorney**
12. ☐ **English Translation Document** *(if applicable)*
13. ☐ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
14. ☐ **Preliminary Amendment**
15. ☐ **Return Receipt Postcard** *(MPEP § 503) (Should be specifically itemized)*
16. ☐ **Certified Copy of Priority Document(s)** *(if foreign priority is claimed)*
17. ☐ **Nonpublication Request**
    Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. ☑ **Other:** Authorization Under 37 C.F.R. 1.136(a)(3)
    Certification and Request for Prioritized Examination
    Under 37 CFR 1.102(e)

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

☑ The address associated with Customer Number: 153767 **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/John M. Covert, #38,759/	Date	Aug. 24, 2018
Name (Print/Type)	John M. Covert	Registration No. (Attorney/Agent)	38,759

Addendum

ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

==

Sequence Listing was accepted.

See attached Validation Report.

If you need help call the Patent Electronic Business Center at (866) 217-9197 (toll free).

Reviewer: Saleem, Syed (ASRC)

Timestamp: [year=2018; month=8; day=29; hr=10; min=16; sec=54; ms=751;]

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Validated By CRFValidator v 1.0.5

Application No: 16112453 Version No: 1.0

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Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Stephen Donald WILTON	Nonprovisional Application Number (if known):	
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:

I. ☑ **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /John M. Covert, #38,759/	Date Aug. 24, 2018
Name (Print/Typed) John M. Covert	Practitioner Registration Number 38,759

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *Total of ______ forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: WILTON *et al.*	Confirmation No.: *To Be Assigned*
Applicant: The University of Western Australia	Art Unit: *To Be Assigned*
Application No.: *To Be Assigned*	Examiner: *To Be Assigned*
Filed: August 24, 2018	Atty. Docket: 4140.01500B1

Title: **ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF**

Authorization to Treat a Reply as Incorporating an Extension of Time Under 37 C.F.R. § 1.136(a)(3)

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

The U.S. Patent and Trademark Office is hereby authorized to treat any concurrent or future reply that requires a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. The U.S. Patent and Trademark Office is hereby authorized to charge all required extension of time fees to our Deposit Account No. 19-0036, if such fees are not otherwise provided for in such reply.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

John M. Covert

John M. Covert
Attorney for Applicant
Registration No. 38,759

Date: Aug. 24, 2018

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
9894726_1.docx

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4140.01500B1
	Application Number	
Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Stephen	Donald	WILTON	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Applecross	Country of Residence i	AU

Mailing Address of Inventor:

Address 1	18 Spey Road		
Address 2			
City	Applecross	State/Province	
Postal Code	6153	Country i	AU

Inventor 2 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sue		FLETCHER	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Bayswater	Country of Residence i	AU

Mailing Address of Inventor:

Address 1	14 Roberts Street		
Address 2			
City	Bayswater	State/Province	
Postal Code	6053	Country i	AU

Inventor 3 — Remove

Legal Name

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4140.01500B1
	Application Number	
Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Graham		MCCLOREY	

Residence Information (Select One) ◯ US Residency ◉ Non US Residency ◯ Active US Military Service

City	Bayswater	Country of Residence i	AU

Mailing Address of Inventor:

Address 1	8 Digwood Close		
Address 2			
City	Bayswater	State/Province	
Postal Code	6053	Country i	AU

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	153767
Email Address	Add Email Remove Email

Application Information:

Title of the Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF		
Attorney Docket Number	4140.01500B1	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	22	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country i

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4140.01500B1
	Application Number	

Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	153767		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	15274772	2016-09-23

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15274772	Continuation of	14740097	2015-06-15	9605262	2017-03-28

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14740097	Continuation of	13741150	2013-01-14

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13741150	Continuation of	13168857	2011-06-24

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4140.01500B1
	Application Number	

Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13168857	Continuation of	12837359	2010-07-15	8232384	2012-07-31
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
12837359	Continuation of	11570691	2008-01-15	7807816	2010-10-05

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
11570691	a 371 of international	PCT/AU2005/000943	2005-06-28

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
2004903474	AU	2004-06-28	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4140.01500B1
	Application Number	
Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4140.01500B1
	Application Number	
Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

- (●) Assignee
- ( ) Legal Representative under 35 U.S.C. 117
- ( ) Joint Inventor
- ( ) Person to whom the inventor is obligated to assign.
- ( ) Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	The University of Western Australia

Mailing Address Information For Applicant:

Address 1	35 Stirling Highway		
Address 2			
City	Crawley	**State/Province**	
Country	AU	Postal Code	6009
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4140.01500B1
	Application Number	
Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	The University of Western Australia

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	35 Stirling Highway		
Address 2			
City	Crawley	**State/Province**	
Country i	AU	Postal Code	6009
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/John M. Covert, #38,759/			Date (YYYY-MM-DD)	2018-08-24
First Name	John	Last Name	Covert	Registration Number	38759

Additional Signature may be generated within this form by selecting the Add button.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4140.01500B1
	Application Number	

Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application No. 15/274,772, filed September 23, 2016, now pending, which application is a continuation of U.S. Patent Application No. 14/740,097, filed June 15, 2015, now issued as U.S. Patent No. 9,605,262, which application is a continuation of U.S. Patent Application No. 13/741,150, filed January 14, 2013, now abandoned, which application is a continuation of U.S. Patent Application No. 13/168,857, filed June 24, 2011, now abandoned, which application is a continuation of U.S. Patent Application No. 12/837,359, filed July 15, 2010, now issued as U.S. Patent No. 8,232,384, which application is a continuation of U.S. Patent Application No. 11/570,691, filed January 15, 2008, now issued as U.S. Patent No. 7,807,816, which application is a 35 U.S.C. § 371 National Phase Application of PCT/AU2005/000943, filed June 28, 2005, which claims priority to Australian Patent Application No. 2004903474, filed June 28, 2004; which applications are each incorporated herein by reference in their entireties.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

This invention was made with government support under grant number R01 NS044146 awarded by the National Institutes of Health. The government has certain rights in the invention.

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with the application is provided in text format in liew of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is 4140.01500B1_SL.txt. The text file is 62,078 bytes, was created on August 23, 2018 and is being submitted electronically via EFS-Web.

FIELD OF THE INVENTION

The present invention relates to novel antisense compounds and compositions suitable for facilitating exon skipping. It also provides methods for inducing exon skipping using the novel antisense compounds as well as therapeutic compositions adapted for use in the methods of the invention.

BACKGROUND ART

Significant effort is currently being expended researching methods for suppressing or compensating for disease-causing mutations in genes. Antisense technologies are being developed using a range of chemistries to affect gene expression at a variety of different levels (transcription, splicing, stability, translation). Much of that research has focused on the use of antisense compounds to correct or compensate for abnormal or disease-associated genes in a myriad of different conditions.

Antisense molecules are able to inhibit gene expression with exquisite specificity and because of this many research efforts concerning oligonucleotides as modulators of gene expression have focused on inhibiting the expression of targeted genes such as oncogenes or viral genes. The antisense oligonucleotides are directed either against RNA (sense strand) or against DNA where they form triplex structures inhibiting transcription by RNA polymerase II. To achieve a desired effect in specific gene down-regulation, the oligonucleotides must either promote the decay of the targeted mRNA or block translation of that mRNA, thereby effectively preventing *de novo* synthesis of the undesirable target protein.

Such techniques are not useful where the object is to up-regulate production of the native protein or compensate for mutations which induce premature termination of translation such as nonsense or frame-shifting mutations. Furthermore, in cases where a normally functional protein is prematurely terminated because of mutations therein, a means for restoring some functional protein production through antisense technology has been shown to be possible through intervention during the splicing processes (Sierakowska H, *et al.*, (1996) Proc Natl Acad Sci USA 93, 12840-12844; Wilton SD, *et al.*, (1999)

Neuromusc Disorders 9, 330-338; van Deutekom JC *et al.*, (2001) Human Mol Genet 10, 1547-1554). In these cases, the defective gene transcript should not be subjected to targeted degradation so the antisense oligonucleotide chemistry should not promote target mRNA decay.

In a variety of genetic diseases, the effects of mutations on the eventual expression of a gene can be modulated through a process of targeted exon skipping during the splicing process. The splicing process is directed by complex multi-particle machinery that brings adjacent exon-intron junctions in pre-mRNA into close proximity and performs cleavage of phosphodiester bonds at the ends of the introns with their subsequent reformation between exons that are to be spliced together. This complex and highly precise process is mediated by sequence motifs in the pre-mRNA that are relatively short semi-conserved RNA segments to which bind the various nuclear splicing factors that are then involved in the splicing reactions. By changing the way the splicing machinery reads or recognises the motifs involved in pre-mRNA processing, it is possible to create differentially spliced mRNA molecules. It has now been recognised that the majority of human genes are alternatively spliced during normal gene expression, although the mechanisms invoked have not been identified. Using antisense oligonucleotides, it has been shown that errors and deficiencies in a coded mRNA could be bypassed or removed from the mature gene transcripts.

In nature, the extent of genetic deletion or exon skipping in the splicing process is not fully understood, although many instances have been documented to occur, generally at very low levels (Sherrat TG, *et al.*, (1993) Am J Hum Genet 53, 1007-1015). However, it is recognised that if exons associated with disease-causing mutations can be specifically deleted from some genes, a shortened protein product can sometimes be produced that has similar biological properties of the native protein or has sufficient biological activity to ameliorate the disease caused by mutations associated with the target exon (Lu QL, *et al.*, (2003) Nature Medicine 9, 1009-1014; Aartsma-Rus A *et al.*, (2004) Am J Hum Genet 74: 83-92).

This process of targeted exon skipping is likely to be particularly useful in long genes where there are many exons and introns, where there is redundancy in the genetic constitution of the exons or where a protein is able to function without one or more particular exons (*e.g.* with the dystrophin gene, which consists of 79 exons; or possibly some collagen genes which encode for repeated blocks of sequence or the huge nebulin or titin genes which are comprised of ~80 and over 370 exons, respectively).

Efforts to redirect gene processing for the treatment of genetic diseases associated with truncations caused by mutations in various genes have focused on the use of antisense oligonucleotides that either: (1) fully or partially overlap with the elements involved in the splicing process; or (2) bind to the pre-mRNA at a position sufficiently close to the element to disrupt the binding and function of the splicing factors that would normally mediate a particular splicing reaction which occurs at that element (*e.g.*, binds to the pre-mRNA at a position within 3, 6, or 9 nucleotides of the element to be blocked).

For example, modulation of mutant dystrophin pre-mRNA splicing with antisense oligoribonucleotides has been reported both *in vitro* and *in vivo*. In one type of dystrophin mutation reported in Japan, a 52-base pair deletion mutation causes exon 19 to be removed with the flanking introns during the splicing process (Matsuo *et al.*, (1991) J Clin Invest., 87:2127-2131). An *in vitro* minigene splicing system has been used to show that a 31-mer 2'-O-methyl oligoribonucleotide complementary to the 5' half of the deleted sequence in dystrophin Kobe exon 19 inhibited splicing of wild-type *pre-mRNA* (Takeshima *et al.* (1995), J. Clin. Invest., 95, 515-520). The same oligonucleotide was used to induce exon skipping from the native dystrophin gene transcript in human cultured lymphoblastoid cells.

Dunckley *et al.*, (1997) Nucleosides & Nucleotides, 16, 1665-1668 described *in vitro* constructs for analysis of splicing around exon 23 of mutated dystrophin in the *mdx* mouse mutant, a model for muscular dystrophy. Plans to analyse these constructs *in vitro* using 2' modified oligonucleotides targeted to splice sites within and adjacent to mouse dystrophin exon 23 were discussed, though no target sites or sequences were given.

2'-O-methyl oligoribonucleotides were subsequently reported to correct dystrophin deficiency in myoblasts from the *mdx* mouse from this group. An antisense oligonucleotide targeted to the 3' splice site of murine dystrophin intron 22 was reported to cause skipping of the mutant exon as well as several flanking exons and created a novel in-frame dystrophin transcript with a novel internal deletion. This mutated dystrophin was expressed in 1-2% of antisense treated mdx myotubes. Use of other oligonucleotide modifications such as 2'-O-methoxyethyl phosphodiesters are described (Dunckley *et al.* (1998) Human Mol. Genetics, 5, 1083-90).

Thus, antisense molecules may provide a tool in the treatment of genetic disorders such as Duchenne Muscular Dystrophy (DMD). However, attempts to induce exon skipping using antisense molecules have had mixed success. Studies on dystrophin exon 19, where successful skipping of that exon from the dystrophin pre-mRNA was achieved using a variety of antisense molecules directed at the flanking splice sites or motifs within the exon involved in exon definition as described by Errington *et al.* (2003) J Gen Med 5, 518-527".

In contrast to the apparent ease of exon 19 skipping, the first report of exon 23 skipping in the *mdx* mouse by Dunckley *et al.*, (1998) is now considered to be reporting only a naturally occurring revertant transcript or artefact rather than any true antisense activity. In addition to not consistently generating transcripts missing exon 23, Dunckley *et al.*, (1998) did not show any time course of induced exon skipping, or even titration of antisense oligonucleotides, to demonstrate dose dependent effects where the levels of exon skipping corresponded with increasing or decreasing amounts of antisense oligonucleotide. Furthermore, this work could not be replicated by other researchers.

The first example of specific and reproducible exon skipping in the *mdx* mouse model was reported by Wilton *et al.*, (1999) Neuromuscular Disorders 9, 330-338. By directing an antisense molecule to the donor splice site, consistent and efficient exon 23 skipping was induced in the dystrophin mRNA within 6 hours of treatment of the cultured cells. Wilton *et al*, (1999), also describe targeting the acceptor region of the mouse dystrophin pre-mRNA with longer antisense oligonucleotides and being unable to repeat

the published results of Dunckley *et al.*, (1998). No exon skipping, either 23 alone or multiple removal of several flanking exons, could be reproducibly detected using a selection of antisense oligonucleotides directed at the acceptor splice site of intron 22.

While the first antisense oligonucleotide directed at the intron 23 donor splice site induced consistent exon skipping in primary cultured myoblasts, this compound was found to be much less efficient in immortalized cell cultures expressing higher levels of dystrophin. However, with refined targeting and antisense oligonucleotide design, the efficiency of specific exon removal was increased by almost an order of magnitude (see Mann CJ *et al.*, (2002) J Gen Med 4, 644-654).

Thus, there remains a need to provide antisense oligonucleotides capable of binding to and modifying the splicing of a target nucleotide sequence. Simply directing the antisense oligonucleotides to motifs presumed to be crucial for splicing is no guarantee of the efficacy of that compound in a therapeutic setting.

SUMMARY OF THE INVENTION

The present invention provides antisense molecule compounds and compositions suitable for binding to RNA motifs involved in the splicing of pre-mRNA that are able to induce specific and efficient exon skipping and a method for their use thereof.

The choice of target selection plays a crucial role in the efficiency of exon skipping and hence its subsequent application of a potential therapy. Simply designing antisense molecules to target regions of pre-mRNA presumed to be involved in splicing is no guarantee of inducing efficient and specific exon skipping. The most obvious or readily defined targets for splicing intervention are the donor and acceptor splice sites although there are less defined or conserved motifs including exonic splicing enhancers, silencing elements and branch points.

The acceptor and donor splice sites have consensus sequences of about 16 and 8 bases respectively (see Figure 1 for schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process).

According to a first aspect, the invention provides antisense molecules capable of binding to a selected target to induce exon skipping.

For example, to induce exon skipping in exons 3 to 8, 10 to 16, 19 to 40, 42 to 44, 46, 47, and 50 to 53 in the Dystrophin gene transcript the antisense molecules are preferably selected from the group listed in Table 1A.

In a further example, it is possible to combine two or more antisense oligonucleotides of the present invention together to induce multiple exon skipping in exons 19-20, and 53. This is a similar concept to targeting of a single exon. A combination or "cocktail" of antisense oligonucleotides are directed at adjacent exons to induce efficient exon skipping.

In another example, to induce exon skipping in exons 19-20, 31, 34 and 53 it is possible to improve exon skipping of a single exon by joining together two or more antisense oligonucleotide molecules. This concept is termed by the inventor as a "weasel", an example of a cunningly designed antisense oligonucleotide. A similar concept has been described in Aartsma-Rus A *et al.*, (2004) Am J Hum Genet 74: 83-92).

According to a second aspect, the present invention provides antisense molecules selected and or adapted to aid in the prophylactic or therapeutic treatment of a genetic disorder comprising at least an antisense molecule in a form suitable for delivery to a patient.

According to a third aspect, the invention provides a method for treating a patient suffering from a genetic disease wherein there is a mutation in a gene encoding a particular protein and the affect of the mutation can be abrogated by exon skipping, comprising the steps of: (a) selecting an antisense molecule in accordance with the methods described herein; and (b) administering the molecule to a patient in need of such treatment.

The invention also addresses the use of purified and isolated antisense oligonucleotides of the invention, for the manufacture of a medicament for treatment of a genetic disease.

The invention further provides a method of treating a condition characterised by Duchenne muscular dystrophy, which method comprises administering to

a patient in need of treatment an effective amount of an appropriately designed antisense oligonucleotide of the invention, relevant to the particular genetic lesion in that patient. Further, the invention provides a method for prophylactically treating a patient to prevent or at least minimise Duchene muscular dystrophy, comprising the step of: administering to the patient an effective amount of an antisense oligonucleotide or a pharmaceutical composition comprising one or more of these biological molecules.

The invention also provides kits for treating a genetic disease, which kits comprise at least a antisense oligonucleotide of the present invention, packaged in a suitable container and instructions for its use.

Other aspects and advantages of the invention will become apparent to those skilled in the art from a review of the ensuing description, which proceeds with reference to the following figures.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 Schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process (SEQ ID NOS: 213 and 214).

Figure 2. Diagrammatic representation of the concept of antisense oligonucleotide induced exon skipping to by-pass disease-causing mutations (not drawn to scale). The hatched box represents an exon carrying a mutation that prevents the translation of the rest of the mRNA into a protein. The solid black bar represents an antisense oligonucleotide that prevents inclusion of that exon in the mature mRNA.

Figure 3 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. The preferred compound [H8A(-06+18)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured normal human muscle cells. The less preferred antisense oligonucleotide [H8A(-06+14)] also induces efficient exon skipping, but at much higher concentrations. Other antisense

oligonucleotides directed at exon 8 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

Figure 4 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at internal domains within exon 7, presumably exon splicing enhancers. The preferred compound [H7A(+45+67)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells. The less preferred antisense oligonucleotide [H7A(+2+26)] induces only low levels of exon skipping at the higher transfection concentrations. Other antisense oligonucleotides directed at exon 7 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

Figure 5 Gel electrophoresis showing an example of low efficiency exon 6 skipping using two non-preferred antisense molecules directed at human exon 6 donor splice site. Levels of induced exon 6 skipping are either very low [H6D(+04-21)] or almost undetectable [H6D(+18-04)]. These are examples of non-preferred antisense oligonucleotides to demonstrate that antisense oligonucleotide design plays a crucial role in the efficacy of these compounds.

Figure 6 Gel electrophoresis showing strong and efficient human exon 6 skipping using an antisense molecules [H6A(+69+91)] directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells.

Figure 7 Gel electrophoresis showing strong human exon 4 skipping using an antisense molecule H4A(+13+32) directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells,

Figure 8A	Gel electrophoresis showing strong human exon 12 skipping using antisense molecule H12A(+52+75) directed at exon 12 internal domain.
Figure 8B	Gel electrophoresis showing strong human exon 11 skipping using antisense molecule H11A(+75+97) directed at an exon 11 internal domain.
Figure 9A	Gel electrophoresis showing strong human exon 15 skipping using antisense molecules H15A(+48+71) and H15A(-12+19) directed at an exon 15 internal domain.
Figure 9B	Gel electrophoresis showing strong human exon 16 skipping using antisense molecules H16A(-12+19) and H16A(-06+25).
Figure 10	Gel electrophoresis showing human exon 19/20 skipping using antisense molecules H20A(+44+71) and H20A(+149+170) directed at an exon 20 and a "cocktail" of antisense oligonucleotides H19A(+35+65, H20A(+44+71) and H20A(+149+170) directed at exons 19/20.
Figure 11	Gel electrophoresis showing human exon 19/20 skipping using "weasels" directed at exons 19 and 20.
Figure 12	Gel electrophoresis showing exon 22 skipping using antisense molecules H22A(+125+106), H22A(+47+69), H22A(+80+101) and H22D(+13-11) directed at exon 22.
Figure 13	Gel electrophoresis showing exon 31 skipping using antisense molecules H31D(+01-25) and H31D(+03-22); and a "cocktail" of antisense molecules directed at exon 31.
Figure 14	Gel electrophoresis showing exon 33 skipping using antisense molecules H33A(+30+56) and H33A(+64+88) directed at exon 33.
Figure 15	Gel electrophoresis showing exon 35 skipping using antisense molecules H35A(+141+161), H35A(+116+135), and H35A(+24+43) and a "cocktail of two antisense molecules, directed at exon 35.
Figure 16	Gel electrophoresis showing exon 36 skipping using antisense molecules H32A(+49+73) and H36A(+26+50) directed at exon 36.

Figure 17 Gel electrophoresis showing exon 37 skipping using antisense molecules H37A(+82+105) and H37A(+134+157) directed at exon 37.

Figure 18 Gel electrophoresis showing exon 38 skipping using antisense molecule H38A(+88+112) directed at exon 38.

Figure 19 Gel electrophoresis showing exon 40 skipping using antisense molecule H40A(-05+17) directed at exon 40.

Figure 20 Gel electrophoresis showing exon 42 skipping using antisense molecule H42A(-04+23) directed at exon 42.

Figure 21 Gel electrophoresis showing exon 46 skipping using antisense molecule H46A(+86+115) directed a# exon 46

Figure 22 Gel electrophoresis showing exon 51, exon 52 and exon 53 skipping using various antisense molecules directed at exons 51, 52 and 53, respectively. A "cocktail" of antisense molecules is also shown directed at exon 53.

BRIEF DESCRIPTION OF THE SEQUENCE LISTINGS

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
1	H8A(-06+18)	GAU AGG UGG UAU CAA CAU CUG UAA
2	H8A (-03+18)	GAU AGG UGG UAU CAA CAU CUG
3	H8A(-07+18)	GAU AGG UGG UAU CAA CAU CUG UAA G
4	H8A(-06+14)	GGU GGU AUC AAC AUC UGU AA
5	H8A(-10+10)	GUA UCA ACA UCU GUA AGC AC
6	H7A(+45+67)	UGC AUG UUC CAG UCG UUG UGU GG
7	H7A(+02+26)	CAC UAU UCC AGU CAA AUA GGU CUG G
8	H7D(+15-10)	AUU UAC CAA CCU UCA GGA UCG AGU A
9	H7A(-18+03)	GGC CUA AAA CAC AUA CAC AUA
10	C6A(-10+10)	CAU UUU UGA CCU ACA UGU GG
11	C6A(-14+06)	UUU GAC CUA CAU GUG GAA AG
12	C6A(-14+12)	UAC AUU UUU GAC CUA CAU GUG GAA AG
13	C6A(-13+09)	AUU UUU GAC CUA CAU GGG AAA G
14	CH6A(+69+91)	UAC GAG UUG AUU GUC GGA CCC AG
15	C6D(+12-13)	GUG GUC UCC UUA CCU AUG ACU GUG G
16	C6D(+06-11)	GGU CUC CUU ACC UAU GA
17	H6D(+04-21)	UGU CUC AGU AAU CUU CUU ACC UAU
18	H6D(+18-04)	UCU UAC CUA UGA CUA UGG AUG AGA

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
19	H4A(+13+32)	GCA UGA ACU CUU GUG GAU CC
20	H4D(+04-16)	CCA GGG UAC UAC UUA CAU UA
21	H4D(-24-44)	AUC GUG UGU CAC AGC AUC CAG
22	H4A(+11+40)	UGU UCA GGG CAU GAA CUC UUG UGG AUC CUU
23	H3A(+30+60)	UAG GAG GCG CCU CCC AUC CUG UAG GUC ACU G
24	H3A(+35+65)	AGG UCU AGG AGG CGC CUC CCA UCC UGU AGG U
25	H3A(+30+54)	GCG CCU CCC AUC CUG UAG GUC ACU G
26	H3D(+46-21)	CUU CGA GGA GGU CUA GGA GGC GCC UC
27	H3A(+30+50)	CUC CCA UCC UGU AGG UCA CUG
28	H3D(+19-03)	UAC CAG UUU UUG CCC UGU CAG G
29	H3A(-06+20)	UCA AUA UGC UGC UUC CCA AAC UGA AA
30	H3A(+37+61)	CUA GGA GGC GCC UCC CAU CCU GUA G
31	H5A(+20+50)	UUA UGA UUU CCA UCU ACG AUG UCA GUA CUU C
32	H5D(+25-05)	CUU ACC UGC CAG UGG AGG AUU AUA UUC CAA A
33	H5D(+10-15)	CAU CAG GAU UCU UAC CUG CCA GUG G
34	H5A(+10+34)	CGA UGU CAG UAC UUC CAA UAU UCA C
35	H5D(-04-21)	ACC AUU CAU CAG GAU UCU
36	H5D(+16-02)	ACC UGC CAG UGG AGG AUU
37	H5A(-07+20)	CCA AUA UUC ACU AAA UCA ACC UGU UAA
38	H5D(+18-12)	CAG GAU UGU UAC CUG CCA GUG GAG GAU UAU
39	H5A(+05+35)	ACG AUG UCA GUA CUU CCA AUA UUC ACU AAA U
40	H5A(+15+45)	AUU UCC AUC UAC GAU GUC AGU ACU UCC AAU A
41	H10A(-05+16)	CAG GAG CUU CCA AAU GCU GCA
42	H10A(-05+24)	CUU GUC UUC AGG AGC UUC CAA AUG CUG CA
43	H10A(+98+119)	UCC UCA GCA GAA AGA AGC CAC G
44	H10A(+130+149)	UUA GAA AUC UCU CCU UGU GC
45	H10A(-33-14)	UAA AUU GGG UGU UAC ACA AU
46	H11D(+26+49)	CCC UGA GGC AUU CCC AUC UUG AAU
47	H11D(+11-09)	AGG ACU UAC UUG CUU UGU UU
48	H11A(+118+140)	CUU GAA UUU AGG AGA UUC AUC UG
49	H11A(+75+97)	CAU CUU CUG AUA AUU UUC CUG UU
50	H12A(+52+75)	UCU UCU GUU UUU GUU AGC CAG UCA
51	H12A(-10+10)	UCU AUG UAA ACU GAA AAU UU

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
52	H12A(+11+30)	UUC UGG AGA UCC AUU AAA AC
53	H13A(+77+100)	CAG CAG UUG CGU GAU CUC CAC UAG
54	H13A(+55+75)	UUC AUC AAC UAC CAC CAC CAU
55	H13D(+06-19)	CUA AGC AAA AUA AUC UGA CCU UAA G
56	H14A(+37+64)	CUU GUA AAA GAA CCC AGC GGU CUU CUG U
57	H14A(+14+35)	CAU CUA CAG AUG UUU GCC CAU C
58	H14A(+51+73)	GAA GGA UGU CUU GUA AAA GAA CC
59	H14D(-02+18)	ACC UGU UCU UCA GUA AGA CG
60	H14D(+14-10)	CAU GAC ACA CCU GUU CUU CAG UAA
61	H14A(+61+80)	CAU UUG AGA AGG AUG UCU UG
62	H14A(-12+12)	AUC UCC CAA UAC CUG GAG AAG AGA
63	H15A(-12+19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA CAU U
64	H15A(+48+71)	UCU UUA AAG CCA GUU GUG UGA AUC
65	H15A(+08+28)	UUU CUG AAA GCC AUG CAC UAA
66	H15D(+17-08)	GUA CAU ACG GCC AGU UUU UGA AGA C
67	H16A(-12+19)	CUA GAU CCG CUU UUA AAA CCU GUU AAA ACA A
68	H16A(-06+25)	UCU UUU CUA GAU CCG CUU UUA AAA CCU GUU A
69	H16A(-06+19)	CUA GAU CCG CUU UUA AAA CCU GUU A
70	H16A(+87+109)	CCG UCU UCU GGG UCA CUG ACU UA
71	H16A(-07+19)	CUA GAU CCG CUU UUA AAA CCU GUU AA
72	H16A(-07+13)	CCG CUU UUA AAA CCU GUU AA
73	H16A(+12+37)	UGG AUU GCU UUU UCU UUU CUA GAU CC
74	H16A(+92+116)	CAU GCU UCC GUC UUC UGG GUC ACU G
75	H16A(+45+67)	G AUC UUG UUU GAG UGA AUA CAG U
76	H16A(+105+126)	GUU AUC CAG CCA UGC UUC CGU C
77	H16D(+05-20)	UGA UAA UUG GUA UCA CUA ACC UGU G
78	H16D(+12-11)	GUA UCA CUA ACC UGU GCU GUA C
79	H19A(+35+53)	CUG CUG GCA UCU UGC AGU U
80	H19A(+35+65)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U
81	H20A(+44+71)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C
82	H20A(+147+168)	CAG CAG UAG UUG UCA UCU GCU C
83	H20A(+185+203)	UGA UGG GGU GGU GGG UUG G
84	H20A(-08+17)	AUC UGC AUU AAC ACC CUC UAG AAA G
85	H20A(+30+53)	CCG GCU GUU CAG UUG UUC UGA GGC
86	H20A(-11+17)	AUC UGC AUU AAC ACC CUC UAG AAA GAA A
87	H20D(+08-20)	GAA GGA GAA GAG AUU CUU ACC UUA CAA A
88	H20A(+44+63)	AUU CGA UCC ACC GGC UGU UC

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
89	H20A(+149+168	CAG CAG UAG UUG UCA UCU GC
90	H21A(-06+16)	GCC GGU UGA CUU CAU CCU GUG C
91	H21A(+85+106)	CUG CAU CCA GGA ACA UGG GUC C
92	H21A(+85+108)	GUC UGC AUC CAG GAA CAU GGG UC
93	H21A(+08+31)	GUU GAA GAU CUG AUA GCC GGU UGA
94	H21D(+18-07)	UAC UUA CUG UCU GUA GCU CUU UCU
95	H22A(+22+45)	CAC UCA UGG UCU CCU GAU AGC GCA
96	H22A(+125+106)	CUG CAA UUC CCC GAG UCU CUG C
97	H22A(+47+69)	ACU GCU GGA CCC AUG UCC UGA UG
98	H22A(+80+101)	CUA AGU UGA GGU AUG GAG AGU
99	H22D(+13-11)	UAU UCA CAG ACC UGC AAU UCC CC
100	H23A(+34+59)	ACA GUG GUG CUG AGA UAG UAU AGG CC
101	H23A(+18+39)	UAG GCC ACU UUG UUG CUC UUG C
102	H23A(+72+90)	UUC AGA GGG CGC UUU CUU C
103	H24A(+48+70)	GGG CAG GCC AUU CCU CCU UCA GA
104	H24A(-02+22)	UCU UCA GGG UUU GUA UGU GAU UCU
105	H25A(+9+36)	CUG GGC UGA AUU GUC UGA AUA UCA CUG
106	H25A(+131+156)	CUG UUG GCA CAU GUG AUC CCA CUG AG
107	H25D(+16-08)	GUC UAU ACC UGU UGG CAC AUG UGA
108	H26A(+132+156)	UGC UUU CUG UAA UUC AUC UGG AGU U
109	H26A(-07+19)	CCU CCU UUC UGG CAU AGA CCU UCC AC
110	H26A(+68+92)	UGU GUC AUC CAU UCG UGC AUC UCU G
111	H27A(+82+106)	UUA AGG CCU CUU GUG CUA CAG GUG G
112	H27A(-4+19)	GGG GCU CUU CUU UAG CUC UCU GA
113	H27D(+19-03)	GAC UUC CAA AGU CUU GCA UUU C
114	H28A(-05+19)	GCC AAC AUG CCC AAA CUU CCU AAG
115	H28A(+99+124)	CAG AGA UUU CCU CAG CUC CGC CAG GA
116	H28D(+16-05)	CUU ACA UCU AGC ACC UCA GAG
117	H29A(+57+81)	UCC GCC AUC UGU UAG GGU CUG UGC C
118	H29A(+18+42)	AUU UGG GUU AUC CUC UGA AUG UCG C
119	H29D(+17-05)	CAU ACC UCU UCA UGU AGU UCC C
120	H30A(+122+147)	CAU UUG AGC UGC GUC CAC CUU GUC UG
121	H30A(+25+50)	UCC UGG GCA GAC UGG AUG CUC UGU UC
122	H30D(+19-04)	UUG CCU GGG CUU CCU GAG GCA UU
123	H31D(+06-18)	UUC UGA AAU AAC AUA UAC CUG UGC
124	H31D(+03-22)	UAG UUU CUG AAA UAA CAU AUA CCU G
125	H31A(+05+25)	GAC UUG UCA AAU CAG AUU GGA
126	H31D(+04-20)	GUU UCU GAA AUA ACA UAU ACC UGU
127	H32D(+04-16)	CAC CAG AAA UAC AUA CCA CA
128	H32A(+151+170)	CAA UGA UUU AGC UGU GAC UG
129	H32A(+10+32)	CGA AAC UUC AUG GAG ACA UCU UG

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
130	H32A(+49+73)	CUU GUA GAC GCU GCU CAA AAU UGG C
131	H33D(+09-11)	CAU GCA CAC ACC UUU GCU CC
132	H33A(+53+76)	UCU GUA CAA UCU GAC GUC CAG UCU
133	H33A(+30+56)	GUC UUU AUC ACC AUU UCC ACU UCA GAC
134	H33A(+64+88)	CCG UCU GCU UUU UCU GUA CAA UCU G
135	H34A(+83+104)	UCC AUA UCU GUA GCU GCC AGC C
136	H34A(+143+165)	CCA GGC AAC UUC AGA AUC CAA AU
137	H34A(-20+10)	UUU CUG UUA CCU GAA AAG AAU UAU AAU GAA
138	H34A(+46+70)	CAU UCA UUU CCU UUC GCA UCU UAC G
139	H34A(+95+120)	UGA UCU CUU UGU CAA UUC CAU AUC UG
140	H34D(+10-20)	UUC AGU GAU AUA GGU UUU ACC UUU CCC CAG
141	H34A(+72+96)	CUG UAG CUG CCA GCC AUU CUG UCA AG
142	H35A(+141+161)	UCU UCU GCU CGG GAG GUG ACA
143	H35A(+116+135)	CCA GUU ACU AUU CAG AAG AC
144	H35A(+24+43)	UCU UCA GGU GCA CCU UCU GU
145	H36A(+26+50)	UGU GAU GUG GUC CAC AUU CUG GUC A
146	H36A(-02+18)	CCA UGU GUU UCU GGU AUU CC
147	H37A(+26+50)	CGU GUA GAG UCC ACC UUU GGG CGU A
148	H37A(+82+105)	UAC UAA UUU CCU GCA GUG GUC ACC
149	H37A(+134+157)	UUC UGU GUG AAA UGG CUG CAA AUC
150	H38A(-01+19)	CCU UCA AAG GAA UGG AGG CC
151	H38A(+59+83)	UGC UGA AUU UCA GCC UCC AGU GGU U
152	H38A(+88+112)	UGA AGU CUU CCU CUU UCA GAU UCA C
153	H39A(+62+85)	CUG GCU UUC UCU CAU CUG UGA UUC
154	H39A(+39+58)	GUU GUA AGU UGU CUC CUC UU
155	H39A(+102+121)	UUG UCU GUA ACA GCU GCU GU
156	H39D(+10-10)	GCU CUA AUA CCU UGA GAG CA
157	H40A(-05+17)	CUU UGA GAC CUC AAA UCC UGU U
158	H40A(+129+153)	CUU UAU UUU CCU UUC AUC UCU GGG C
159	H42A(-04+23)	AUC GUU UCU UCA CGG ACA GUG UGC UGG
160	H42A(+86+109)	GGG CUU GUG AGA CAU GAG UGA UUU
161	H42D(+19-02)	A CCU UCA GAG GAC UCC UCU UGC
162	H43D(+10-15)	UAU GUG UUA CCU ACC CUU GUC GGU C
163	H43A(+101+120)	GGA GAG AGC UUC CUG UAG CU
164	H43A(+78+100)	UCA CCC UUU CCA CAG GCG UUG CA
165	H44A(+85+104)	UUU GUG UCU UUC UGA GAA AC
166	H44D(+10-10)	AAA GAC UUA CCU UAA GAU AC
167	H44A(-06+14)	AUC UGU CAA AUC GCC UGC AG
168	H46D(+16-04)	UUA CCU UGA CUU GCU CAA GC

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
169	H46A(+90+109)	UCC AGG UUC AAG UGG GAU AC
170	H47A(+76+100)	GCU CUU CUG GGC UUA UGG GAG CAC U
171	H47D(+25-02)	ACC UUU AUC CAC UGG AGA UUU GUC UGC
172	H47A(-9+12)	UUC CAC CAG UAA CUG AAA CAG
173	H50A(+02+30)	CCA CUC AGA GCU CAG AUC UUC UAA CUU CC
174	H50A(+07+33)	CUU CCA CUC AGA GCU CAG AUC UUC UAA
175	H50D(+07-18)	GGG AUC CAG UAU ACU UAC AGG CUC C
176	H51A(-01+25)	ACC AGA GUA ACA GUC UGA GUA GGA GC
177	H51D(+16-07)	CUC AUA CCU UCU GCU UGA UGA UC
178	H51A(+111 +134)	UUC UGU CCA AGC CCG GUU GAA AUC
179	H51A(+61+90)	ACA UCA AGG AAG AUG GCA UUU CUA GUU UGG
180	H51A(+66+90)	ACA UCA AGG AAG AUG GCA UUU CUA G
181	H51A(+66+95)	CUC CAA CAU CAA GGA AGA UGG CAU UUC UAG
182	H51D(+08-17)	AUC AUU UUU UCU CAU ACC UUC UGC U
183	H51A/D(+08-17) & (-15+)	AUC AUU UUU UCU CAU ACC UUC UGC UAG GAG CUA AAA
184	H51A(+175+195)	CAC CCA CCA UCA CCC UCU GUG
185	H51A(+199+220)	AUC AUC UCG UUG AUA UCC UCA A
186	H52A(-07+14)	UCC UGC AUU GUU GCC UGU AAG
187	H52A(+12+41)	UCC AAC UGG GGA CGC CUC UGU UCC AAA UCC
188	H52A(+17+37)	ACU GGG GAC GCC UCU GUU CCA
189	H52A(+93+112)	CCG UAA UGA UUG UUC UAG CC
190	H52D(+05-15)	UGU UAA AAA ACU UAC UUC GA
191	H53A(+45+69)	CAU UCA ACU GUU GCC UCC GGU UCU G
192	H53A(+39+62)	CUG UUG CCU CCG GUU CUG AAG GUG
193	H53A(+39+69)	CAU UCA ACU GUU GCC UCC GGU UCU GAA GGU G
194	H53D(+14-07)	UAC UAA CCU UGG UUU CUG UGA
195	H53A(+23+47)	CUG AAG GUG UUC UUG UAC UUC AUC C
196	H53A(+150+176)	UGU AUA GGG ACC CUC CUU CCA UGA CUC
197	H53D(+20-05)	CUA ACC UUG GUU UCU GUG AUU UUC U
198	H53D(+09-18)	GGU AUC UUU GAU ACU AAC CUU GGU UUC
199	H53A(-12+10)	AUU CUU UCA ACU AGA AUA AAA G
200	H53A(-07+18)	GAU UCU GAA UUC UUU CAA CUA GAA U
201	H53A(+07+26)	AUC CCA CUG AUU CUG AAU UC
202	H53A(+124+145)	UUG GCU CUG GCC UGU CCU AAG A
203	H46A(+86+115)	CUC UUU UCC AGG UUC AAG UGG GAU ACU AGC

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
204	H46A(+107+137)	CAA GCU UUU CUU UUA GUU GCU GCU CUU UUC C
205	H46A(-10+20)	UAU UCU UUU GUU CUU CUA GCC UGG AGA AAG
206	H46A(+50+77)	CUG CUU CCU CCA ACC AUA AAA CAA AUU C
207	H45A(-06+20)	CCA AUG CCA UCC UGG AGU UCC UGU AA
208	H45A(+91 +110)	UCC UGU AGA AUA CUG GCA UC
209	H45A(+125+151)	UGC AGA CCU CCU GCC ACC GCA GAU UCA
210	H45D(+16 -04)	CUA CCU CUU UUU UCU GUC UG
211	H45A(+71+90)	UGU UUU UGA GGA UUG CUG AA

Table 1A: Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
81 82	H20A(+44+71) H20A(+147+168)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C CAG CAG UAG UUG UCA UCU GCU C
80 81 82	H19A(+35+65) H20A(+44+71) H20A(+147+168)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U CUG GCA GAA UUC GAU CCA CCG GCU GUU C CAG CAG UAG UUG UCA UCU GCU C
194 195 196	H53D(+14-07) H53A(+23+47) H53A(+150+175)	UAC UAA CCU UGG UUU CUG UGA CUG AAG GUG UUC UUG UAC UUC AUC C UGU AUA GGG ACC CUC CUU CCA UGA CUC

Table 1B: Description of a cocktail of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

SEQ ID	**SEQUENCE**	**NUCLEOTIDE SEQUENCE (5'-3')**
81 82	H20A(+44+71)- H20A(+147+168)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C- CAG CAG UAG UUG UCA UCU GCU C

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
80 88 79	H19A(+35+65)- H20A(+44+63)- H20A(+149+168)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U -AUU CGA UCC ACC GGC UGU UC- CUG CUG GCA UCU UGC AGU U
80 88	H19A(+35+65)- H20A(+44+63)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U -AUU CGA UCC ACC GGC UGU UC-
80 79	H19A(+35+65)- H20A(+149+168)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U -CUG CUG GCA UCU UGC AGU U
138 139	H34A(+46+70)- H34A(+94+120)	CAU UCA UUU CCU UUC GCA UCU UAC G- UGA UCU CUU UGU CAA UUC CAU AUC UG
124 144	H31D(+03-22)- UU- H35A(+24+43)	UAG UUU CUG AAA UAA CAU AUA CCU G- UU- UCU UCA GGU GCA CCU UCU GU
195 196 <u>194</u>	H53A(+23+47)- AA- H53A(+150+175)- AA- H53D(+14-07)	CUG AAG GUG UUC UUG UAC UUC AUC C- UGU AUA GGG ACC CUC CUU CCA UGA CUC- AA- UAC UAA CCU UGG UUU CUG UGA
- <u>212</u>	Aimed at exons 19/20/20	CAG CAG UAG UUG UCA UCU GCU CAA CUG GCA GAA UUC GAU CCA CCG GCU GUU CAA GCC UGA GCU GAU CUG CUC GCA UCU UGC AGU

Table 1C: Description of a "weasel" of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

DETAILED DESCRIPTION OF THE INVENTION

<u>General</u>

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variation and modifications. The invention also includes all of the steps, features, compositions and compounds referred to

or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally equivalent products, compositions and methods are clearly within the scope of the invention as described herein.

Sequence identity numbers (SEQ ID NO:) containing nucleotide and amino acid sequence information included in this specification are collected at the end of the description and have been prepared using the programme PatentIn Version 3.0. Each nucleotide or amino acid sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (*e.g.* <210>1, <210>2, etc.). The length, type of sequence and source organism for each nucleotide or amino acid sequence are indicated by information provided in the numeric indicator fields <211>, <212> and <213>, respectively. Nucleotide and amino acid sequences referred to in the specification are defined by the information provided in numeric indicator field <400> followed by the sequence identifier (*e.g.* <400>1, <400>2, etc.).

An antisense molecules nomenclature system was proposed and published to distinguish between the different antisense molecules (see Mann *et al.*, (2002) J Gen Med 4, 644-654). This nomenclature became especially relevant when testing several slightly different antisense molecules, all directed at the same target region, as shown below:

H # A/D (x : y).

The first letter designates the species (*e.g.* H: human, M: murine, C: canine) "#" designates target dystrophin exon number.

"A/D" indicates acceptor or donor splice site at the beginning and end of the exon, respectively.

(x y) represents the annealing coordinates where "-" or "+" indicate intronic or exonic sequences respectively. As an example, A(-6+18) would indicate the last 6 bases of the intron preceding the target exon and the first 18 bases of the target exon. The closest

splice site would be the acceptor so these coordinates would be preceded with an "A". Describing annealing coordinates at the donor splice site could be D(+2-18) where the last 2 exonic bases and the first 18 intronic bases correspond to the annealing site of the antisense molecule. Entirely exonic annealing coordinates that would be represented by A(+65+85), that is the site between the 65th and 85th nucleotide from the start of that exon.

The entire disclosures of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference. No admission is made that any of the references constitute prior art or are part of the common general knowledge of those working in the field to which this invention relates.

As used necessarily herein the term "derived" and "derived from" shall be taken to indicate that a specific integer may be obtained from a particular source *albeit* not directly from that source.

Throughout this specification, unless the context requires o#herwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

DESCRIPTION OF THE PREFERRED EMBODIMENT

When antisense molecule(s) are targeted to nucleotide sequences involved in splicing in exons within pre-mRNA sequences, normal splicing of the exon may be inhibited causing the splicing machinery to by-pass the entire mutated exon from the mature mRNA. The concept of antisense oligonucleotide induced exon skipping is shown in Figure 2. In many genes, deletion of an entire exon would lead to the production of a non-functional protein through the loss of important functional domains or the disruption of

the reading frame. In some proteins, however, it is possible to shorten the protein by deleting one or more exons, without disrupting the reading frame, from within the protein without seriously altering the biological activity of the protein. Typically, such proteins have a structural role and or possess functional domains at their ends. The present invention describes antisense molecules capable of binding to specified dystrophin pre-mRNA targets and re-directing processing of that gene.

Antisense Molecules

According to a first aspect of the invention, there is provided antisense molecules capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules are preferably selected from the group of compounds shown in Table 1A. There is also provided a combination or "cocktail" of two or more antisense oligonucleotides capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules in a "cocktail" are preferably selected from the group of compounds shown in Table 1B. Alternatively, exon skipping may be induced by antisense oligonucleotides joined together "weasels" preferably selected from the group of compounds shown in Table 1C.

Designing antisense molecules to completely mask consensus splice sites may not necessarily generate any skipping of the targeted exon. Furthermore, the inventors have discovered that size or length of the antisense oligonucleotide itself is not always a primary factor when designing antisense molecules. With some targets such as exon 19, antisense oligonucleotides as short as 12 bases were able to induce exon skipping, *albeit* not as efficiently as longer (20-31 bases) oligonucleotides. In some other targets, such as murine dystrophin exon 23, antisense oligonucleotides only 17 residues long were able to induce more efficient skipping than another overlapping compound of 25 nucleotides.

The inventors have also discovered that there does not appear to be any standard motif that can be blocked or masked by antisense molecules to redirect splicing. In some exons, such as mouse dystrophin exon 23, the donor splice site was the most

amenable to target to re-direct skipping of that exon. It should be noted that designing and testing a series of exon 23 specific antisense molecules to anneal to overlapping regions of the donor splice site showed considerable variation in the efficacy of induced exon skipping. As reported in Mann *et al.*, (2002) there was a significant variation in the efficiency of bypassing the nonsense mutation depending upon antisense oligonucleotide annealing ("Improved antisense oligonucleotide induced exon skipping in the *mdx* mouse model of muscular dystrophy". J Gen Med 4: 644-654). Targeting the acceptor site of exon 23 or several internal domains was not found to induce any consistent exon 23 skipping.

In other exons targeted for removal, masking the donor splice site did not induce any exon skipping. However, by directing antisense molecules to the acceptor splice site (human exon 8 as discussed below), strong and sustained exon skipping was induced. It should be noted that removal of human exon 8 was tightly linked with the co-removal of exon 9. There is no strong sequence homology between the exon 8 antisense oligonucleotides and corresponding regions of exon 9 so it does not appear to be a matter of cross reaction. Rather the splicing of these two exons is inextricably linked. This is not an isolated instance as the same effect is observed in canine cells where targeting exon 8 for removal also resulted in the skipping of exon 9. Targeting exon 23 for removal in the mouse dystrophin pre-mRNA also results in the frequent removal of exon 22 as well. This effect occurs in a dose dependent manner and also indicates close coordinated processing of 2 adjacent exons.

In other targeted exons, antisense molecules directed at the donor or acceptor splice sites did not induce exon skipping while annealing antisense molecules to intra-exonic regions (*i.e.* exon splicing enhancers within human dystrophin exon 6) was most efficient at inducing exon skipping. Some exons, both mouse and human exon 19 for example, are readily skipped by targeting antisense molecules to a variety of motifs. That is, targeted exon skipping is induced after using antisense oligonucleotides to mask donor and acceptor splice sites or exon splicing enhancers.

To identify and select antisense oligonucleotides suitable for use in the modulation of exon skipping, a nucleic acid sequence whose function is to be modulated must first be identified. This may be, for example, a gene (or mRNA transcribed form the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (*i.e.* splice donor sites, splice acceptor sites, or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

Preferably, the present invention aims to provide antisense molecules capable of binding to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping. Duchenne muscular dystrophy arises from mutations that preclude the synthesis of a functional dystrophin gene product. These Duchenne muscular dystrophy gene defects are typically nonsense mutations or genomic rearrangements such as deletions, duplications or micro-deletions or insertions that disrupt the reading frame. As the human dystrophin gene is a large and complex gene with the 79 exons being spliced together to generate a mature mRNA with an open reading frame of approximately 11,000 bases, there are many positions where these mutations can occur. Consequently, a comprehensive antisense oligonucleotide based therapy to address many of the different disease-causing mutations in the dystrophin gene will require that many exons can be targeted for removal during the splicing process.

Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (*i.e.* splice donor sites, splice acceptor sites or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides which can hydrogen bond with each other. Thus, "specifically hybridisable" and "complementary" are terms which are used to indicate a sufficient degree of

complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an antisense molecule need not be 100% complementary to that of its target sequence to be specifically hybridisable. An antisense molecule is specifically hybridisable when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under conditions in which specific binding is desired, *i.e.*, under physiological conditions in the case of *in vivo* assays or therapeutic treatment, and in the case of *in vitro* assays, under conditions in which the assays are performed.

While the above method may be used to select antisense molecules capable of deleting any exon from within a protein that is capable of being shortened without affecting its biological function, the exon deletion should not lead to a reading frame shift in the shortened transcribed mRNA. Thus, if in a linear sequence of three exons the end of the first exon encodes two of three nucleotides in a codon and the next exon is deleted then the third exon in the linear sequence must start with a single nucleotide that is capable of completing the nucleotide triplet for a codon. If the third exon does not commence with a single nucleotide there will be a reading frame shift that would lead to the generation of truncated or a non-functional protein.

It wilt be appreciated that the codon arrangements at the end of exons in structural proteins may not always break at the end of a codon, consequently there may be a need to delete more than one exon from the pre-mRNA to ensure in-frame reading of the mRNA. In such circumstances, a plurality of antisense oligonucleotides may need to be selected by the method of the invention wherein each is directed to a different region responsible for inducing splicing in the exons that are to be deleted.

The length of an antisense molecule may vary so long as it is capable of binding selectively to the intended location within the pre-mRNA molecule. The length of such sequences can be determined in accordance with selection procedures described herein. Generally, the antisense molecule will be from about 10 nucleotides in length up to

about 50 nucleotides in length. It will be appreciated however that any length of nucleotides within this range may be used in the method. Preferably, the length of the antisense molecule is between 17 to 30 nucleotides in length.

In order to determine which exons can be connected in a dystrophin gene, reference should be made to an exon boundary map. Connection of one exon with another is based on the exons possessing the same number at the 3' border as is present at the 5' border of the exon to which it is being connected. Therefore, if exon 7 were deleted, exon 6 must connect to either exons 12 or 18 to maintain the reading frame. Thus, antisense oligonucleotides would need to be selected which redirected splicing for exons 7 to 11 in the first instance or exons 7 to 17 in the second instance. Another and somewhat simpler approach to restore the reading frame around an exon 7 deletion would be to remove the two flanking exons. Induction of exons 6 and 8 skipping should result in an in-frame transcript with the splicing of exons 5 to 9. In practise however, targeting exon 8 for removal from the pre-mRNA results in the co-removal of exon 9 so the resultant transcript would have exon 5 joined to exon 10. The inclusion or exclusion of exon 9 does not alter the reading frame. Once the antisense molecules to be tested have been identified, they are prepared according to standard techniques known in the art. The most common method for producing antisense molecules is the methylation of the 2' hydroxyribose position and the incorporation of a phosphorothioate backbone produces molecules that superficially resemble RNA but that are much more resistant to nuclease degradation.

To avoid degradation of pre-mRNA during duplex formation with the antisense molecules, the antisense molecules used in the method may be adapted to minimise or prevent cleavage by endogenous RNase H. This property is highly preferred as the treatment of the RNA with the unmethylated oligonucleotides either intracellularly or in crude extracts that contain RNase H leads to degradation of the pre-mRNA: antisense oligonucleotide duplexes. Any form of modified antisense molecules that is capable of by-passing or not inducing such degradation may be used in the present method. An example of antisense molecules which when duplexed with RNA are not cleaved by cellular RNase H is 2'-O-methyl derivatives. 2'-O-methyl-oligoribonucleotides are very stable in a cellular

environment and in animal tissues, and their duplexes with RNA have higher Tm values than their ribo- or deoxyribo- counterparts.

Antisense molecules that do not activate RNase H can be made in accordance with known techniques (*see, e.g.*, U.S. Pat. 5,149,797). Such antisense molecules, which may be deoxyribonucleotide or ribonucleotide sequences, simply contain any structural modification which sterically hinders or prevents binding of RNase H to a duplex molecule containing the oligonucleotide as one member thereof, which structural modification does not substantially hinder or disrupt duplex formation. Because the portions of the oligonucleotide involved in duplex formation are substantially different from those portions involved in RNase H binding thereto, numerous antisense molecules that do not activate RNase H are available. For example, such antisense molecules may be oligonucleotides wherein at least one, or all, of the inter-nucleotide bridging phosphate residues are modified phosphates, such as methyl phosphonates, methyl phosphorothioates, phosphoromorpholidates, phosphoropiperazidates and phosphoramidates. For example, every other one of the internucleotide bridging phosphate residues may be modified as described. In another non-limiting example, such antisense molecules are molecules wherein at least one, or all, of the nucleotides contain a 2' lower alkyl moiety (*e.g.*, C_1-C_4, linear or branched, saturated or unsaturated alkyl, such as methyl, ethyl, ethenyl, propyl, 1-propenyl, 2-propenyl, and isopropyl). For example, every other one of the nucleotides may be modified as described.

While antisense oligonucleotides are a preferred form of the antisense molecules, the present invention comprehends other oligomeric antisense molecules, including but not limited to oligonucleotide mimetics such as are described below.

Specific examples of preferred antisense compounds useful in this invention include oligonucleotides containing modified backbones or non-natural inter-nucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes

referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their inter-nucleoside backbone can also be considered to be oligonucleosides.

In other preferred oligonucleotide mimetics, both the sugar and the inter-nucleoside linkage, *i.e.*, the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleo-bases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone.

Modified oligonucleotides may also contain one or more substituted sugar moieties. Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. Certain nucleo-bases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thioether, *e.g.*, hexyl-S-tritylthiol, a thiocholesterol, an aliphatic chain, *e.g.*, dodecandiol or undecyl residues, a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety.

It is not necessary far all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds that are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this invention, are antisense molecules, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, *i.e.*, a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the increased resistance to nuclease degradation, increased cellular uptake, and an additional region for increased binding affinity for the target nucleic acid.

<u>Methods of Manufacturing Antisense Molecules</u>

The antisense molecules used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). One method for synthesising oligonucleotides on a modified solid support is described in U.S. Pat. No. 4,458,066.

Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates ~ and alkylated derivatives. In one such automated embodiment, diethyl-phosphoramidites are used as starting materials and may be synthesized as described by Beaucage, *et al.*, (1981) *Tetrahedron Letters*, 22:1859-1862.

The antisense molecules of the invention are synthesised *in vitro* and do not include antisense compositions of biological origin, or genetic vector constructs designed to direct the *in vivo* synthesis of antisense molecules. The molecules of the invention may also be mixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor

targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption.

Therapeutic Agents

The present invention also can be used as a prophylactic or therapeutic, which may be utilised for the purpose of treatment of a genetic disease.

Accordingly, in one embodiment the present invention provides antisense molecules that bind to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping described herein in a therapeutically effective amount admixed with a pharmaceutically acceptable carrier, diluent, or excipient.

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similarly untoward reaction, such as gastric upset and the like, when administered to a patient. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in Martin, *Remington's Pharmaceutical Sciences*, 18th Ed., Mack Publishing Co., Easton, PA, (1990).

In a more specific form of the invention there are provided pharmaceutical compositions comprising therapeutically effective amounts of an antisense molecule together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (*e.g.*, Tris-HCl, acetate, phosphate), pH and ionic strength and additives such as detergents and solubilizing agents (*e.g.*, Tween 80, Polysorbate 80), anti-oxidants (*e.g.*, ascorbic acid, sodium metabisulfite), preservatives (*e.g.*, Thimersol, benzyl alcohol) and bulking substances (*e.g.*, lactose, mannitol). The material may be incorporated into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into

liposomes. Hylauronic acid may also be used. Such compositions may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the present proteins and derivatives. *See, e.g.*, *Martin, Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 that are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilised form.

It will be appreciated that pharmaceutical compositions provided according to the present invention may be administered by any means known in the art. Preferably, the pharmaceutical compositions for administration are administered by injection, orally, or by the pulmonary, or nasal route. The antisense molecules are more preferably delivered by intravenous, intra-arterial, intraperitoneal, intramuscular, or subcutaneous routes of administration.

<u>Antisense molecule based therapy</u>

Also addressed by the present invention is the use of antisense molecules of the present invention, for manufacture of a medicament for modulation of a genetic disease.

The delivery of a therapeutically useful amount of antisense molecules may be achieved by methods previously published. For example, intracellular delivery of the antisense molecule may be via a composition comprising an admixture of the antisense molecule and an effective amount of a block copolymer. An example of this method is described in US patent application US 20040248833.

Other methods of delivery of antisense molecules to the nucleus are described in Mann CJ *et al.*, (2001) ["*Antisense-induced exon skipping and the synthesis of dystrophin in the mdx mouse*". Proc., Natl. Acad. Science, 98(1) 42-47J and in Gebski etal., (2003). Human Molecular Genetics, 12(15): 1801-1811.

A method for introducing a nucleic acid molecule into a cell by way of an expression vector either as naked DNA or complexed to lipid carriers, is described in US patent US 6,806,084.

It may be desirable to deliver the antisense molecule in a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes or liposome formulations.

Liposomes are artificial membrane vesicles which are useful as delivery vehicles *in vitro* and *in vivo*. These formulations may have net cationic, anionic or neutral charge characteristics and are useful characteristics with *in vitro*, *in vivo* and *ex vivo* delivery methods. It has been shown that large unilamellar vesicles (LUV), which range in size from 0.2-4.0 .PHI.m can encapsulate a substantial percentage of an aqueous buffer containing large macromolecules. RNA, and DNA can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, *et al.*, Trends Biochem. Sci., 6:77, 1981).

In order for a liposome to be an efficient gene transfer vehicle, the following characteristics should be present: (1) encapsulation of the antisense molecule of interest at high efficiency while not compromising their biological activity; (2) preferential and substantial binding to a target cell in comparison to non-target cells; (3) delivery of the aqueous contents of the vesicle to the target cell cytoplasm at high efficiency; and (4) accurate and effective expression of genetic information (Mannino, *et al.*, Biotechniques, 6:682, 1988).

The composition of the liposome is usually a combination of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations.

Alternatively, the antisense construct may be combined with other pharmaceutically acceptable carriers or diluents to produce a pharmaceutical composition. Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition may be formulated for parenteral, intramuscular, intravenous, subcutaneous, intraocular, oral or transdermal administration.

The routes of administration described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and any dosage for any particular animal and condition. Multiple approaches for introducing functional new genetic material into cells, both *in vitro* and *in vivo* have been attempted (Friedmann (1989) Science, 244:1275-1280).

These approaches include integration of the gene to be expressed into modified retroviruses (Friedmann (1989) supra; Rosenberg (1991) Cancer Research 51(18), suppl.: 5074S-5079S); integration into non-retrovirus vectors (Rosenfeld, *et al.* (1992) Cell, 68:143-155; Rosenfeld, *et al.* (1991) Science, 252:431-434); or delivery of a transgene linked to a heterologous promoter-enhancer element via liposomes (Friedmann (1989), supra; Brigham, *et al.* (1989) Am. J. Med. Sci., 298:278-281; Nabel, *et al.* (1990) Science, 249:1285-1288; Hazinski, *et al.* (1991) Am. J. Resp. Cell Molec. Biol., 4:206-209; and Wang and Huang (1987) Proc. Natl. Acad. Sci. (USA), 84:7851-7855); coupled to ligand-specific, cation-based transport systems (Wu and Wu (1988) J. Biol. Chem., 263:14621-14624) or the use of naked DNA, expression vectors (Nabel et al. (1990), supra); Wolff *et al.* (1990) Science, 247:1465-1468). Direct injection of transgenes into tissue produces only localized expression (Rosenfeld (1992) supra); Rosenfeld *et al.* (1991) supra; Brigham *et al.* (1989) supra; Nabel (1990) supra; and Hazinski *et al.* (1991) supra). The Brigham *et al.* group (Am. J. Med. Sci. (1989) 298:278-281 and Clinical Research (1991) 39 (abstract)) have reported *in vivo* transfection only of lungs of mice following either intravenous or intratracheal administration of a DNA liposome complex. An example of a review article of human gene therapy procedures is: Anderson, Science (1992) 256:808-813.

The antisense molecules of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the

compounds of the invention, pharmaceutically acceptable salts of such pro-drugs, and other bioequivalents.

The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: *i.e.*, salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

For oligonucleotides, preferred examples of pharmaceutically acceptable salts include but are not limited to (a) salts formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, malefic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polygiutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine. The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including rectal delivery), pulmonary, *e.g.*, by inhalation or insufflation of powders or aerosols, (including by nebulizer, intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intra-arterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Oligonucleotides with at least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration.

The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of

bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Kits of the Invention

The invention also provides kits for treatment of a patient with a genetic disease which kit comprises at least an antisense molecule, packaged in a suitable container, together with instructions for its use.

In a preferred embodiment, the kits will contain at least one antisense molecule as shown in Table 1A, or a cocktail of antisense molecules as shown in Table 1B or a "weasel" compound as shown in Table 1C. The kits may also contain peripheral reagents such as buffers, stabilizers, etc.

Those of ordinary skill in the field should appreciate that applications of the above method has wide application for identifying antisense molecules suitable for use in the treatment of many other diseases.

EXAMPLES

The following Examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these Examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. The references cited herein are expressly incorporated by reference.

Methods of molecular cloning, immunology and protein chemistry, which are not explicitly described in the following examples, are reported in the literature and are known by those skilled in the art. General texts that described conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art, included, for example: Sambrook *et al*, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (1989);

Glover ed., *DNA Cloning: A Practical Approach*, Volumes I and II, MRL Press, Ltd., Oxford, U.K. (1985); and Ausubel, F., Brent, R., Kingston, R.E., Moore, D.D., Seidman, J.G., Smith, J.A., Struhl, K. *Current Protocols in Molecular Biology*. Greene Publishing Associates/Wiley Intersciences, New York (2002).

DETERMINING INDUCED EXON SKIPPING IN HUMAN MUSCLE CELLS

Attempts by the inventors to develop a rational approach in antisense molecules design were not completely successful as there did not appear to be a consistent trend that could be applied to all exons. As such, the identification of the most effective and therefore most therapeutic antisense molecules compounds has been the result of empirical studies.

These empirical studies involved the use of computer programs to identify motifs potentially involved in the splicing process. Other computer programs were also used to identify regions of the pre-mRNA which may not have had extensive secondary structure and therefore potential sites for annealing of antisense molecules. Neither of these approaches proved completely reliable in designing antisense oligonucleotides for reliable and efficient induction of exon skipping.

Annealing sites on the human dystrophin pre-mRNA were selected for examination, initially based upon known or predicted motifs or regions involved in splicing. 2OMe antisense oligonucleotides were designed to be complementary to the target sequences under investigation and were synthesised on an Expedite 8909 Nucleic Acid Synthesiser. Upon completion of synthesis, the oligonucleotides were cleaved from the support column and de-protected in ammonium hydroxide before being desalted. The quality of the oligonucleotide synthesis was monitored by the intensity of the trityl signals upon each deprotection step during the synthesis as detected in the synthesis log. The concentration of the antisense oligonucleotide was estimated by measuring the absorbance of a diluted aliquot at 260nm.

Specified amounts of the antisense molecules were then tested for their ability to induce exon skipping in an *in vitro* assay, as described below.

Briefly, normal primary myoblast cultures were prepared from human muscle biopsies obtained after informed consent. The cells were propagated and allowed to differentiate into myotubes using standard culturing techniques. The cells were then transfected with the antisense oligonucleotides by delivery of the oligonucleotides to the dells as cationic lipoplexes, mixtures of antisense molecules or cationic liposome preparations.

The cells were then allowed to grow for another 24 hours, after which total RNA was extracted and molecular analysis commenced. Reverse transcriptase amplification (RT-PCR) was undertaken to study the targeted regions of the dystrophin pre-mRNA or induced exonic re-arrangements.

For example, in the testing of an antisense molecule for inducing exon 19 skipping the RT-PCR test scanned several exons to detect involvement of any adjacent exons. For example, when inducing skipping of exon 19, RT-PCR was carried out with primers that amplified across exons 17 and 21. Amplifications of even larger products in this area (*i.e.* exons 13-26) were also carried out to ensure that there was minimal amplification bias for the shorter induced skipped transcript. Shorter or exon skipped products tend to be amplified more efficiently and may bias the estimated of the normal and induced transcript.

The sizes of the amplification reaction products were estimated on an agarose gel and compared against appropriate size standards. The final confirmation of identity of these products was carried out by direct DNA sequencing to establish that the correct or expected exon junctions have been maintained.

Once efficient exon skipping had been induced with one antisense molecule, subsequent overlapping antisense molecules may be synthesized and then evaluated in the assay as described above. Our definition of an efficient antisense molecule is one that induces strong and sustained exon skipping at transfection concentrations in the order of 300 nM or less.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 8

Antisense oligonucleotides directed at exon 8 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 3 shows differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. H8A(-06+18) [SEQ ID NO:1], which anneals to the last 6 bases of intron 7 and the first 18 bases of exon 8, induces substantial exon 8 and 9 skipping when delivered into cells at a concentration of 20 nM. The shorter antisense molecule, H8A(-06+14) [SEQ ID NO: 4] was only able to induce exon 8 and 9 skipping at 300 nM, a concentration some 15 fold higher than H8A(-06+18), which is the preferred antisense molecule.

This data shows that some particular antisense molecules induce efficient exon skipping while another antisense molecule, which targets a near-by or overlapping region, can be much less efficient. Titration studies show one compound is able to induce targeted exon skipping at 20 nM while the less efficient antisense molecules only induced exon skipping at concentrations of 300 nM and above. Therefore, we have shown that targeting of the antisense molecules to motifs involved in the splicing process plays a crucial role in the overall efficacy of that compound.

Efficacy refers to the ability to induce consistent skipping of a target exon. However, sometimes skipping of the target exons is consistently associated with a flanking exon. That is, we have found that the splicing of some exons is tightly linked. For example, in targeting exon 23 in the mouse model of muscular dystrophy with antisense molecules directed at the donor site of that exon, dystrophin transcripts missing exons 22 and 23 are frequently detected. As another example, when using an antisense molecule directed to exon 8 of the human dystrophin gene, all induced transcripts are missing both exons 8 and 9. Dystrophin transcripts missing only exon 8 are not observed.

Table 2 below discloses antisense molecule sequences that induce exon 8 (and 9) skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
1	H8A(-06+18)	5'-GAU AGG UGG UAU CAA CAU CUG UAA	Very strong to 20 nM
2	H8A (-03+18)	5'-GAU AGG UGG UAU CAA CAU CUG	Very strong skipping to 40nM
3	H8A(-07+18)	5'-GAU AGG UGG UAU CAA CAU CUG UAA G	Strong skipping to 40nM
4	H8A(-06+14)	5'-GGU GGU AUC AAC AUC UGU AA	Skipping to 300nM
5	H8A(-10+10)	5'-GUA UCA ACA UCU GUA AGC AC	Patchy/weak skipping to 100nm

Table 2

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 7

Antisense oligonucleotides directed at exon 7 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 4 shows the preferred antisense molecule, H7A(+45+67) [SEQ ID NO: 6], and another antisense molecule, H7A(+2+26) [SEQ ID NO: 7], inducing exon 7 skipping. Nested amplification products span exons 3 to 9. Additional products above the induced transcript missing exon 7 arise from amplification from carry-over outer primers from the RT-PCR as well as heteroduplex formation.

Table 3 below discloses antisense molecule sequences for induced exon 7 skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
6	H7A(+45+67)	5' - UGC AUG UUC CAG UCG UUG UGU GG	Strong skipping to 20nM
7	H7A(+02+26)	5' - CAC UAU UCC AGU CAA AUA GGU CUG G	Weak skipping at 100nM
8	H7D(+15-10)	5' -AUU UAC CAA CCU UCA GGA UCG AGU A	Weak skipping to 300nM
9	H7A(-18+03)	5' - GGC CUA AAA CAC AUA CAC AUA	Weak skipping to 300nM

Table 3

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 6

Antisense oligonucleotides directed at exon 6 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 5 shows an example of two non-preferred antisense molecules inducing very low levels of exon 6 skipping in cultured human cells. Targeting this exon for specific removal was first undertaken during a study of the canine model using the oligonucleotides as listed in Table 4, below. Some of the human specific oligonucleotides were also evaluated, as shown in Figure 5. In this example, both antisense molecules target the donor splice site and only induced low levels of exon 6 skipping. Both H6D(+4-21) [SEQ ID NO: 17] and H6D(+18-4) [SEQ ID NO: 18] would be regarded as non-preferred antisense molecules.

One antisense oligonucleotide that induced very efficient exon 6 skipping in the canine model, C6A(+69+91) [SEQ ID NO: 14], would anneal perfectly to the corresponding region in human dystrophin exon 6. This compound was evaluated, found to be highly efficient at inducing skipping of that target exon, as shown in Figure 6 and is regarded as the preferred compound for induced exon 6 skipping. Table 4 below discloses antisense molecule sequences for induced exon 6 skipping.

SEQ ID	Antisense Oligo name	Sequence	Ability to induce skipping
10	C6A(-10+10)	5' CAU UUU UGA CCU ACA UGU GG	No skipping
11	C6A(-14+06)	5' UUU GAC CUA CAU GUG GAA AG	No skipping
12	C6A(-14+12)	5' UAC AUU UUU GAC CUA CAU GUG GAA AG	No skipping
13	C6A(-13+09)	5' AUU UUU GAC CUA CAU GGG AAA G	No skipping
14	CH6A(+69+91)	5' UAC GAG UUG AUU GUC GGA CCC AG	Strong skipping to 20 nM
15	C6D(+12-13)	5' GUG GUC UCC UUA CCU AUG ACU GUG G	Weak skipping at 300 nM
16	C6D(+06-11)	5' GGU CUC CUU ACC UAU GA	No skipping
17	H6D(+04-21)	5' UGU CUC AGU AAU CUU CUU ACC UAU	Weak skipping to 50 nM
18	H6D(+18-04)	5' UCU UAC CUA UGA CUA UGG AUG AGA	Very weak skipping to 300 nM

Table 4

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 4

Antisense oligonucleotides directed at exon 4 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 7 shows an example of a preferred antisense molecule inducing skipping of exon 4 skipping in cultured human cells. In this example, one preferred antisense compound, H4A(+13+32) [SEQ ID NO:19], which targeted a presumed exonic splicing enhancer induced efficient exon skipping at a concentration of 20 nM while other non-preferred antisense oligonucleotides failed to induce even low levels of exon 4 skipping. Another preferred antisense molecule inducing skipping of exon 4 was H4A(+111+40) [SEQ ID NO:22], which induced efficient exon skipping at a concentration of 20 nM.

Table 5 below discloses antisense molecule sequences for inducing exon 4 skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
19	H4A(+13+32)	5' GCA UGA ACU CUU GUG GAU CC	Skipping to 20 nM
22	H4A(+11+40)	5' UGU UCA GGG CAU GAA CUC UUG UGG AUC CUU	Skipping to 20 nM
20	H4D(+04-16)	5' CCA GGG UAC UAC UUA CAU UA	No skipping
21	H4D(-24-44)	5' AUC GUG UGU CAC AGC AUC CAG	No skipping

Table 5

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 3

Antisense oligonucleotides directed at exon 3 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H3A(+30+60) [SEQ ID NO:23] induced substantial exon 3 skipping when delivered into cells at a concentration of 20 nM to 600 nM. The antisense molecule, H3A(+35+65) [SEQ ID NO: 24] induced exon skipping at 300 nM.

Table 6 below discloses antisense molecule sequences that induce exon 3 skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
23	H3A(+30+60)	UAG GAG GCG CCU CCC AUC CUG UAG GUC ACU G	Moderate skipping to 20 to 600 nM
24	H3A(+35+65)	AGG UCU AGG AGG CGC CUC CCA UCC UGU AGG U	Working to 300 nM
25	H3A(+30+54)	GCG CCU CCC AUC CUG UAG GUC ACU G	Moderate 100-600 nM
26	H3D(+46-21)	CUU CGA GGA GGU CUA GGA GGC GCC UC	No skipping
27	H3A(+30+50)	CUC CCA UCC UGU AGG UCA CUG	Moderate 20-600 nM
28	H3D(+19-03)	UAC CAG UUU UUG CCC UGU CAG G	No skipping
29	H3A(-06+20)	UCA AUA UGC UGC UUCCCA AAC UGA AA	No skipping

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
30	H3A(+37+61)	CUA GGA GGC GCC UCC CAU CCU GUA G	No skipping

Table 6

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 5

Antisense oligonucleotides directed at exon 5 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H5A(+20+50) [SEQ ID NO:31] induces substantial exon 5 skipping when delivered into cells at a concentration of 100 nM. Table 7 below shows other antisense molecules tested. The majority of these antisense molecules were not as effective at exon skipping as H5A(+20+50). However, H5A(+15+45) [SEQ ID NO: 40] was able to induce exon 5 skipping at 300 nM.

Table 7 below discloses antisense molecule sequences that induce exon 5 skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
31	H5A(+20+50)	UUA UGA UUU CCA UCU ACG AUG UCA GUA CUU C	Working to 100 nM
32	H5D(+25-05)	CUU ACC UGC CAG UGG AGG AUU AUA UUC CAA A	No skipping
33	H5D(+10-15)	CAU CAG GAU UCU UAC CUG CCA GUG G	Inconsistent at 300 nM
34	H5A(+10+34)	CGA UGU CAG UAC UUC CAA UAU UCA C	Very weak
35	H5D(-04-21)	ACC AUU CAU CAG GAU UCU	No skipping
36	H5D(+16-02)	ACC UGC CAG UGG AGG AUU	No skipping
37	H5A(-07+20)	CCA AUA UUC ACU AAA UCA ACC UGU UAA	No skipping
38	H5D(+18-12)	CAG GAU UCU UAC CUG CCA GUG GAG GAU UAU	No skipping

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
39	H5A(+05+35)	ACG AUG UCA GUA CUU CCA AUA UUC ACU AAA U	No skipping
40	H5A(+15+45)	AUU UCC AUC UAC GAU GUC AGU ACU UCC AAU A	Working to 300 nM

Table 7

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 10

Antisense oligonucleotides directed at exon 10 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H10A(-05+16) [SEQ ID NO:41] induced substantial exon 10 skipping when delivered into cells. Table 8 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was variable. Table 8 below discloses antisense molecule sequences that induce exon 10 skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
41	H10A(-05+16)	CAG GAG CUU CCA AAU GCU GCA	Not tested
42	H10A(-05+24)	CUU GUC UUC AGG AGC UUC CAA AUG CUG CA	Not tested
43	H10A(+98+119)	UCC UCA GCA GAA AGA AGC CAC G	Not tested
44	H10A(+130+149)	UUA GAA AUC UCU CCU UGU GC	No skipping
45	H10A(-33-14)	UAA AUU GGG UGU UAC ACA AU	No skipping

Table 8

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 11

Antisense oligonucleotides directed at exon 11 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 8B shows an example of H11A(+75+97) [SEQ ID NO:49] antisense molecule inducing exon 11 skipping in cultured human cells. H11A(+75+97) induced substantial exon 11 skipping when delivered into cells at a concentration of 5 nM. Table 9

below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was observed at 100 nM.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
46	H11D(+26+49)	CCC UGA GGC AUU CCC AUC UUG AAU	Skipping at 100 nM
47	H11D(+11-09)	AGG ACU UAC UUG CUU UGU UU	Skipping at 100 nM
48	H11A(+118+140)	CUU GAA UUU AGG AGA UUC AUC UG	Skipping at 100 nM
49	H11A(+75+97)	CAU CUU CUG AUA AUU UUC CUG UU	Skipping at 100 nM
46	H11D(+26+49)	CCC UGA GGC AUU CCC AUC UUG AAU	Skipping at 5nM

Table 9

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 12

Antisense oligonucleotides directed at exon 12 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H12A(+52+75) [SEQ ID NO:50] induced substantial exon 12 skipping when delivered into cells at a concentration of 5 nM, as shown in Figure 8A. Table 10 below shows other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The antisense molecules ability to induce exon skipping was variable.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
50	H12A(+52+75)	UCU UCU GUU UUU GUU AGC CAG UCA	Skipping at 5 nM
51	H12A(-10+10)	UCU AUG UAA ACU GAA AAU UU	Skipping at 100 nM
52	H12A(+11+30)	UUC UGG AGA UCC AUU AAA AC	No skipping

Table 10

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 13

Antisense oligonucleotides directed at exon 13 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H13A(+77+100) [SEQ ID NO:53] induced substantial exon 13 skipping when delivered into cells at a concentration of 5 nM. Table 11 below includes two other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These other antisense molecules were unable to induce exon skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
53	H13A(+77+100)	CAG CAG UUG CGU GAU CUC CAC UAG	Skipping at 5 nM
54	H13A(+55+75)	UUC AUC AAC UAC CAC CAC CAU	No skipping
55	H13D(+06-19)	CUA AGC AAA AUA AUC UGA CCU UAA G	No skipping

Table 11

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 14

Antisense oligonucleotides directed at exon 14 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H14A(+37+64) [SEQ ID NO:56] induced weak exon 14 skipping when delivered into cells at a concentration of 100 nM. Table 12 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
56	H14A(+37+64)	CUU GUA AAA GAA CCC AGC GGU CUU CUG U	Skipping at 100 nM

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
57	H14A(+14+35)	CAU CUA CAG AUG UUU GCC CAU C	No skipping
58	H14A(+51+73)	GAA GGA UGU CUU GUA AAA GAA CC	No skipping
59	H14D(-02+18)	ACC UGU UCU UCA GUA AGA CG	No skipping
60	H14D(+14-10)	CAU GAC ACA CCU GUU CUU CAG UAA	No skipping
61	H14A(+61 +80)	CAU UUG AGA AGG AUG UCU UG	No skipping
62	H14A(-12+12)	AUC UCC CAA UAC CUG GAG AAG AGA	No skipping

Table 12

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 15

Antisense oligonucleotides directed at exon 15 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H15A(-12+19) [SEQ ID NO:63] and H15A(+48+71) [SEQ ID NO:64] induced substantial exon 15 skipping when delivered into cells at a concentration of 10 Nm, as shown in Figure 9A. Table 13 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 Nm. These other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
63	H15A(-12+19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA CAU U	Skipping at 5Nm
64	H15A(+48+71)	UCU UUA AAG CCA GUU GUG UGA AUC	Skipping at 5Nm
65	H15A(+08+28)	UUU CUG AAA GCC AUG CAC UAA	No skipping
63	H15A(-12+19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA CAU U	No skipping
66	H15D(+17-08)	GUA CAU ACG GCC AGU UUU UGA AGA C	No skipping

Table 13

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 16

Antisense oligonucleotides directed at exon 16 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H16A(-12+19) [SEQ ID NO:67] and H16A(-06+25) [SEQ ID NO:68] induced substantial exon 16 skipping when delivered into cells at a concentration of 10 nM, as shown in Figure 9B. Table 14 below includes other antisense molecules tested. H16A(-06+19) [SEQ ID NO:69] and H16A(+87+109) [SEQ ID NO:70] were tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These two antisense molecules were able to induce exon skipping at 25 nM and 100 nM, respectively. Additional antisense molecules were tested at 100, 200 and 300 nM and did not result in any exon skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
67	H16A(-12+19)	CUA GAU CCG CUU UUA AAA CCU GUU AAA ACA A	Skipping at 5 nM
68	H16A(-06+25)	UCU UUU CUA GAU CCG CUU UUA AAA CCU GUU A	Skipping at 5 nM
69	H16A(-06+19)	CUA GAU CCG CUU UUA AAA CCU GUU A	Skipping at 25 nM
70	H16A(+87+109)	CCG UCU UCU GGG UCA CUG ACU UA	Skipping at 100 nM

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
71	H16A(-07+19)	CUA GAU CCG CUU UUA AAA CCU GUU AA	No skipping
72	H16A(-07+13)	CCG CUU UUA AAA CCU GUU AA	No skipping
73	H16A(+12+37)	UGG AUU GCU UUU UCU UUU CUA GAU CC	No skipping
74	H16A(+92+116)	CAU GCU UCC GUC UUC UGG GUC ACU G	No skipping
75	H16A(+45+67)	G AUC UUG UUU GAG UGA AUA CAG U	No skipping
76	H16A(+105+126)	GUU AUC CAG CCA UGC UUC CGU C	No skipping
77	H16D(+05-20)	UGA UAA UUG GUA UCA CUA ACC UGU G	No skipping
78	H16D(+12-11)	GUA UCA CUA ACC UGU GCU GUA C	No skipping

Table 14

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 19

Antisense oligonucleotides directed at exon 19 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H19A(+35+65) [SEQ ID NO:79] induced substantial exon 19 skipping when delivered into cells at a concentration of 10 nM. This antisense molecule also showed very strong exon skipping at concentrations of 25, 50, 100, 300 and 600 nM.

Figure 10 illustrates exon 19 and 20 skipping using a "cocktail" of antisense oligonucleotides, as tested using gel electrophoresis. It is interesting to note that it was not easy to induce exon 20 skipping using single antisense oligonucleotides H20A(+44+71) [SEQ ID NO:81] or H20A(+149+170) [SEQ ID NO:82], as illustrated in sections 2 and 3 of the gel shown in Figure 10. Whereas, a "cocktail" of antisense oligonucleotides was more efficient as can be seen in section 4 of Figure 10 using a "cocktail" of antisense oligonucleotides H20A(+44+71) and H20A(+149+170). When the cocktail was used to target exon 19, skipping was even stronger (see section 5, Figure 10).

Figure 11 illustrates gel electrophoresis results of exon 19/20 skipping using "weasels" The "weasels" were effective in skipping exons 19 and 20 at concentrations of 25, 50, 100, 300 and 600 nM. A further "weasel" sequence is shown in the last row of Table 3C. This compound should give good results.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 20

Antisense oligonucleotides directed at exon 20 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

None of the antisense oligonucleotides tested induced exon 20 skipping when delivered into cells at a concentration of 10, 25, 50, 300 or 600 nM (see Table 15). Antisense molecules H20A(-11+17) [SEQ ID NO:86] and H20D(+08-20) [SEQ ID NO:87] are yet to be tested.

However, a combination or "cocktail" of H20A(+44+71) [SEQ ID NO: 81] and H20(+149+170) [SEQ ID NO:82] in a ratio of 1:1, exhibited very strong exon skipping at a concentration of 100 nM and 600 nM. Further, a combination of antisense molecules H19A(+35+65) [SEQ ID NO:79], H20A(+44+71) [SEQ ID NO:81] and H20A(+149+170) [SEQ ID NO:82] in a ratio of 2:1:1, induced very strong exon skipping at a concentration ranging from 10 nM to 600 nM.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
81	H20A(+44+71)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C	No skipping
82	H20A(+147+168)	CAG CAG UAG UUG UCA UCU GCU C	No skipping
83	H20A(+185+203)	UGA UGG GGU GGU GGG UUG G	No skipping
84	H20A(-08+17)	AUC UGC AUU AAC ACC CUC UAG AAA G	No skipping
85	H20A(+30+53)	CCG GCU GUU CAG UUG UUC UGA GGC	No skipping
86	H20A(-11+17)	AUC UGC AUU AAC ACC CUC UAG AAA GAA A	Not tested yet
87	H20D(+08-20)	GAA GGA GAA GAG AUU CUU ACC UUA CAA A	Not tested yet
81 & 82	H20A(+44+71) & H20A(+147+168)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C CAG CAG UAG UUG UCA UCU GCU C	Very strong skipping
80, 81	H19A(+35+65);	GCC UGA GCU GAU CUG CUG GCA UCU	Very strong

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
& 82	H20A(+44+71); H20A(+147+168)	UGC AGU U; CUG GCA GAA UUC GAU CCA CCG GCU GUU C; CAG CAG UAG UUG UCA UCU GCU C	skipping

Table 15

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 21

Antisense oligonucleotides directed at exon 21 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H21A(+85+108) [SEQ ID NO:92] and H21A(+85+106) [SEQ ID NO:91] induced exon 21 skipping when delivered into cells at a concentration of 50 nM. Table 16 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
90	H21A(-06+16)	GCC GGU UGA CUU CAU CCU GUG C	Skips at 600 nM
91	H21A(+85+106)	CUG CAU CCA GGA ACA UGG GUC C	Skips at 50 nM
92	H21A(+85+108)	GUC UGC AUC CAG GAA CAU GGG UC	Skips at 50 nM
93	H21A(+08+31)	GUU GAA GAU CUG AUA GCC GGU UGA	Skips faintly to
94	H21D(+18-07)	UAC UUA CUG UCU GUA GCU CUU UCU	No skipping

Table 16

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 22

Antisense oligonucleotides directed at exon 22 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 12 illustrates differing efficiencies of two antisense molecules directed at exon 22 acceptor splice site. H22A(+125+106) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO: 98] induce strong exon 22 skipping from 50 nM to 600 nM concentration.

H22A(+125+146) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO:98] induced exon 22 skipping when delivered into cells at a concentration of 50 nM. Table 17 below shows other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed a variable ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
95	H22A(+22+45)	CAC UCA UGG UCU CCU GAU AGC GCA	No skipping
96	H22A(+125+146)	CUG CAA UUC CCC GAG UCU CUG C	Skipping to 50 nM
97	H22A(+47+69)	ACU GCU GGA CCC AUG UCC UGA UG	Skipping to 300 nM
98	H22A(+80+101)	CUA AGU UGA GGU AUG GAG AGU	Skipping to 50 nM
99	H22D(+13-11)	UAU UCA CAG ACC UGC AAU UCC CC	No skipping

Table 17

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 23

Antisense oligonucleotides directed at exon 23 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 18 below shows antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed no ability to induce exon skipping or are yet to be tested.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
100	H23A(+34+59)	ACA GUG GUG CUG AGA UAG UAU AGG CC	No skipping
101	H23A(+18+39)	UAG GCC ACU UUG UUG CUC UUG C	No Skipping
102	H23A(+72+90)	UUC AGA GGG CGC UUU CUU C	No Skipping

Table 18

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 24

Antisense oligonucleotides directed at exon 24 were prepared using similar methods as described above. Table 19 below outlines the antisense oligonucleotides directed at exon 24 that are yet to be tested for their ability to induce exon 24 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
103	H24A(+48+70)	GGG CAG GCC AUU CCU CCU UCA GA	Needs testing
104	H24A(-02+22)	UCU UCA GGG UUU GUA UGU GAU UCU	Needs testing

Table 19

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 25

Antisense oligonucleotides directed at exon 25 were prepared using similar methods as described above. Table 20 below shows the antisense oligonucleotides directed at exon 25 that are yet to be tested for their ability to induce exon 25 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
105	H25A(+9+36)	CUG GGC UGA AUU GUC UGA AUA UCA CUG	Needs testing
106	H25A(+131+156)	CUG UUG GCA CAU GUG AUC CCA CUG AG	Needs testing
107	H25D(+16-08)	GUC UAU ACC UGU UGG CAC AUG UGA	Needs testing

Table 20

ANTISENSE OLIGONUCIEOTIDES DIRECTED AT EXON 26

Antisense oligonucleotides directed at exon 26 were prepared using similar methods as described above. Table 21 below outlines the antisense oligonucleotides directed at exon 26 that are yet to be tested for their ability to induce exon 26 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
108	H26A(+132+156)	UGC UUU CUG UAA UUC AUC UGG AGU U	Needs testing
109	H26A(-07+19)	CCU CCU UUC UGG CAU AGA CCU UCC AC	Needs testing
110	H26A(+68+92)	UGU GUC AUC CAU UCG UGC AUC UCU G	Faint skipping at 600 nM

Table 21

ANTISENSE OLIQONUCLEOTIDES DIRECTED AT EXON 27

Antisense oligonucleotides directed at exon 27 were prepared using similar methods as described above. Table 22 below outlines the antisense oligonucleotides directed at exon 27 that are yet to be tested for their ability to induce exon 27 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
111	H27A(+82+106)	UUA AGG CCU CUU GUG CUA CAG GUG G	Needs testing
112	H27A(-4+19)	GGG CCU CUU CUU UAG CUC UCU GA	Faint skipping at 600 and 300 nM
113	H27D(+19-03)	GAC UUC CAA AGU CUU GCA UUU C	v. strong skipping at 600 and 300 nM

Table 22

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 28

Antisense oligonucleotides directed at exon 28 were prepared using similar methods as described above. Table 23 below outlines the antisense oligonucleotides directed at exon 28 that are yet to be tested for their ability to induce exon 28 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
114	H28A(-05+19)	GCC AAC AUG CCC AAA CUU CCU AAG	v. strong skipping at 600 and 300 nM
115	H28A(+99+124)	CAG AGA UUU CCU CAG CUC CGC CAG GA	Needs testing
116	H28D(+16-05)	CUU ACA UCU AGC ACC UCA GAG	v. strong skipping at 600 and 300 nM

Table 23

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 29

Antisense oligonucleotides directed at exon 29 were prepared using similar methods as described above. Table 24 below outlines the antisense oligonucleotides directed at exon 29 that are yet to be tested for their ability to induce exon 29 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
117	H29A(+57+81)	UCC GCC AUC UGU UAG GGU CUG UGC C	Needs testing
118	H29A(+18+42)	AUU UGG GUU AUC CUC UGA AUG UCG C	v. strong skipping at 600 and 300 nM
119	H29D(+17-05)	CAU ACC UCU UCA UGU AGU UCC C	v. strong skipping at 600 and 300 nM

Table 24

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 30

Antisense oligonucleotides directed at exon 30 were prepared using similar methods as described above. Table 25 below outlines the antisense oligonucleotides directed at exon 30 that are yet to be tested for their ability to induce exon 30 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
120	H30A(+122+147)	CAU UUG AGC UGC GUC CAC CUU GUC UG	Needs testing
121	H30A(+25+50)	UCC UGG GCA GAC UGG AUG CUC UGU UC	Very strong skipping at 600 and 300 nM.
122	H30D(+19-04)	UUG CCU GGG CUU CCU GAG GCA UU	Very strong skipping at 600 and 300 nM.

Table 25

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 31

Antisense oligonucleotides directed at exon 31 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 13 illustrates differing efficiencies of two antisense molecules directed at exon 31 acceptor splice site and a "cocktail" of exon 31 antisense oligonucleotides at varying concentrations. H31D(+03-22) [SEQ ID NO:124] substantially induced exon 31 skipping when delivered into cells at a concentration of 20 nM. Table 26 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
123	H31D(+06-18)	UUC UGA AAU AAC AUA UAC CUG UGC	Skipping to 300 nM
124	H31D(+03-22)	UAG UUU CUG AAA UAA CAU AUA CCU G	Skipping to 20 nM
125	H31A(+05+25)	GAC UUG UCA AAU CAG AUU GGA	No skipping
126	H31D(+04-20)	GUU UCU GAA AUA ACA UAU ACC UGU	Skipping to 300 nM

Table 26

ANTISENSE OLIGONUCTEOTIDES DIRECTED AT EXON 32

Antisense oligonucleotides directed at exon 32 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H32D(+04-16) [SEQ ID NO:127] and H32A(+49+73) [SEQ ID NO:130] induced exon 32 skipping when delivered into cells at a concentration of 300 nM. Table 27 below also shows other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules did not show an ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
127	H32D(+04-16)	CAC CAG AAA UAC AUA CCA CA	Skipping to 300 nM
128	H32A(+151+170)	CAA UGA UUU AGC UGU GAC UG	No skipping
129	H32A(+10+32)	CGA AAC UUC AUG GAG ACA UCU UG	No skipping
130	H32A(+49+73)	CUU GUA GAC GCU GCU CAA AAU UGG C	Skipping to 300 nM

Table 27

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 33

Antisense oligonucleotides directed at exon 33 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 14 shows differing efficiencies of two antisense molecules directed at exon 33 acceptor splice site. H33A(+64+88) [SEQ ID NO:134] substantially induced exon 33 skipping when delivered into cells at a concentration of 10 nM. Table 28 below includes other antisense molecules tested at a concentration of 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
131	H33D(+09-11)	CAU GCA CAC ACC UUU GCU CC	No skipping
132	H33A(+53+76)	UCU GUA CAA UCU GAC GUC CAG UCU	Skipping to 200 nM
133	H33A(+30+56)	GUG UUU AUC ACC AUU UCC ACU UCA GAC	Skipping to 200 nM
134	H33A(+64+88)	GCG UCU GCU UUU UCU GUA CAA UCU G	Skipping to 10 nM

Table 28

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 34

Antisense oligonucleotides directed at exon 34 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 29 below includes antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
135	H34A(+83+104)	UCC AUA UCU GUA GCU GGC AGC C	No skipping
136	H34A(+143+165)	CCA GGC AAC UUC AGA AUC CAA AU	No skipping
137	H34A(-20+10)	UUU CUG UUA CCU GAA AAG AAU UAU AAU GAA	Not tested
138	H34A(+46+70)	CAU UCA UUU CCU UUC GCA UCU UAC G	Skipping to 300 nM
139	H34A(+95+120)	UGA UCU CUU UGU CAA UUC CAU AUC UG	Skipping to 300 nM
140	H34D(+10-20)	UUC AGU GAU AUA GGU UUU ACC UUU CCC CAG	Not tested
141	H34A(+72+96)	CUG UAG CUG CCA GCC AUU CUG UCA AG	No skipping

Table 29

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 35

Antisense oligonucleotides directed at exon 35 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 15 shows differing efficiencies of antisense molecules directed at exon 35 acceptor splice site. H35A(+24+43) [SEQ ID NO:144] substantially induced exon 35 skipping when delivered into cells at a concentration of 20 nM. Table 30 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed no ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
142	H35A(+141+161)	UCU UCU GCU CGG GAG GUG ACA	Skipping to 20 nM
143	H35A(+116+135)	CCA GUU ACU AUU CAG AAG AC	No skipping
144	H35A(+24+43)	UCU UCA GGU GCA CCU UCU GU	No skipping

Table 30

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 36

Antisense oligonucleotides directed at exon 36 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense molecule H36A(+26+50) [SEQ ID NO:145] induced exon 36 skipping when delivered into cells at a concentration of 300 nM, as shown in Figure 16.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 37

Antisense oligonucleotides directed at exon 37 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 17 shows differing efficiencies of two antisense molecules directed at exon 37 acceptor splice site. H37A(+82+105) [SEQ ID NO:148] and H37A(+134+157)

[SEQ ID NO:149] substantially induced exon 37 skipping when delivered into cells at a concentration of 10 nM. Table 31 below shows the antisense molecules tested.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
147	H37A(+26+50)	CGU GUA GAG UCC ACC UUU GGG CGU A	No skipping
148	H37A(+82+105)	UAC UAA UUU CCU GCA GUG GUC ACC	Skipping to 10 nM
149	H37A(+134+157)	UUC UGU GUG AAA UGG CUG CAA AUC	Skipping to 10 nM

Table 31

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 38

Antisense oligonucleotides directed at exon 38 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 18 illustrates antisense molecule H38A(+88+112) [SEQ ID NO:152] , directed at exon 38 acceptor splice site. H38A(+88+112) substantially induced exon 38 skipping when delivered into cells at a concentration of 10 nM. Table 32 below shows the antisense molecules tested and their ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
150	H38A(-01+19)	CCU UCA AAG GAA UGG AGG CC	No skipping
151	H38A(+59+83)	UGC UGA AUU UCA GCC UCC AGU GGU U	Skipping to 10 nM
152	H38A(+88+112)	UGA AGU CUU CCU CUU UCA GAU UCA C	Skipping to 10 nM

Table 32

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 39

Antisense oligonucleotides directed at exon 39 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H39A(+62+85) [SEQ ID NO:153] induced exon 39 skipping when delivered into cells at a concentration of 100 nM. Table 33 below shows the antisense molecules tested and their ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
153	H39A(+62+85)	CUG GCU UUC UCU CAU CUG UGA UUC	Skipping to 100 nM
154	H39A(+39+58)	GUU GUA AGU UGU CUC CUC UU	No skipping
155	H39A(+102+121)	UUG UCU GUA ACA GCU GCU GU	No skipping
156	H39D(+10-10)	GCU CUA AUA CCU UGA GAG CA	Skipping to 300 nM

Table 33

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 40

Antisense oligonucleotides directed at exon 40 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 19 illustrates antisense molecule H40A(-05+17) [SEQ ID NO:157] directed at exon 40 acceptor splice site. H40A(-05+17) and H40A(+129+153) [SEQ ID NO:158] both substantially induced exon 40 skipping when delivered into cells at a concentration of 5 nM.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 42

Antisense oligonucleotides directed at exon 42 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 20 illustrates antisense molecule H42A(-04+23) [SEQ ID NO:159], directed at exon 42 acceptor splice site. H42A(-4+23) and H42D(+19-02) [SEQ ID NO:161] both induced exon 42 skipping when delivered into cells at a concentration of 5 nM. Table 34 below shows the antisense molecules tested and their ability to induce exon 42 skipping.

SEQ ID	Antisense afigonucleotide name	Sequence	Ability to induce skipping
159	H42A(-4+23)	AUC GUU UCU UCA CGG ACA GUG UGG UGC	Skipping to 5 nM
160	H42A(+86+109)	GGG CUU GUG AGA CAU GAG UGA UUU	Skipping to 100 nM
161	H42D(+19-02)	A CCU UCA GAG GAC UCC UCU UGC	Skipping to 5 nM

Table 34

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 43

Antisense oligonucleotides directed at exon 43 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H43A(+101+120) [SEQ ID NO:163] induced exon 43 skipping when delivered into cells at a concentration of 25 nM. Table 35 below includes the antisense molecules tested and their ability to induce exon 43 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
162	H43D(+10-15)	UAU GUG UUA CCU ACC CUU GUC GGU C	Skipping to 100 nM
163	H43A(+101+120)	GGA GAG AGC UUC CUG UAG CU	Skipping to 25 nM
164	H43A(+78+100)	UCA CCC UUU CCA CAG GCG UUG CA	Skipping to 200 n M

Table 35

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 44

Antisense oligonucleotides directed at exon 44 were prepared using similar methods as described above. Testing fior the ability of these antisense molecules to induce exon 44 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 165 to 167 in Table 1A.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 45

Antisense oligonucleotides directed at exon 45 were prepared using similar methods as described above. Testing for the ability of these antisense molecules to induce exon 45 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 207 to 211 in Table 1A.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 46

Antisense oligonucleotides directed at exon 46 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 21 illustrates the efficiency of one antisense molecule directed at exon 46 acceptor splice site. Antisense oligonucleotide H46A(+86+115) [SEQ ID NO:203] showed very strong ability to induce exon 46 skipping. Table 36 below includes antisense molecules tested. These antisense molecules showed varying ability to induce exon 46 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
168	H46D(+16-04)	UUA CCU UGA CUU GCU CAA GC	No skipping
169	H46A(+90+109)	UCC AGG UUC AAG UGG GAU AC	No skipping
203	H46A(+86+115)	CUC UUU UCC AGG UUC AAG UGG GAU ACU AGC	Good skipping to 100 nM
204	H46A(+107+137)	CAA GCU UUU CUU UUA GUU GCU GCU CUU UUC C	Good skipping to 100 nM
205	H46A(-10+20)	UAU UCU UUU GUU CUU CUA GCC UGG AGA AAG	Weak skipping
206	H46A(+50+77)	CUG CUU CCU CCA ACC AUA AAA CAA AUU C	Weak skipping

Table 36

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 47

Antisense oligonucleotides directed at exon 47 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H47A(+76+100) [SEQ ID NO:170] and H47A(-09+12) [SEQ ID NO:172] both induced exon 47 skipping when delivered into cells at a concentration of 200 nM. H47D(+25-02) [SEQ ID NO: 171] is yet to be prepared and tested.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 50

Antisense oligonucleotides directed at exon 50 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense oligonucleotide molecule H50A(+02+30) [SEQ ID NO: 173] was a strong inducer of exon skipping. Further, H50A(+07+33) [SEQ ID NO:174] and H50D(+07-18) [SEQ ID NO:175] both induced exon 50 skipping when delivered into cells at a concentration of 100 nM.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 51

Antisense oligonucleotides directed at exon 51 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 22 illustrates differing efficiencies of two antisense molecules directed at exon 51 acceptor splice site. Antisense oligonucleotide H51A(+66+90) [SEQ ID NO:180] showed the stronger ability to induce exon 51 skipping. Table 37 below includes antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 51 skipping. The strongest inducers of exon skipping were antisense oligonucleotide H51A(+61+90) [SEQ ID NO: 179] and H51A(+66+95) [SEQ ID NO: 181].

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
176	H51A(-01+25)	ACC AGA GUA ACA GUC UGA GUA GGA GC	Faint skipping
177	H51D(+16-07)	CUC AUA CCU UCU GCU UGA UGA UC	Skipping at 300 nM
178	H51A(+111+134)	UUC UGU CCA AGC CCG GUU GAA AUC	Needs re- testing
179	H51A(+61+90)	ACA UCA AGG AAG AUG GCA UUU CUA GUU UGG	Very strong skipping
180	H51A(+66+90)	ACA UCA AGG AAG AUG GCA UUU CUA G	skipping
181	H51A(+66+95)	CUC CAA CAU CAA GGA AGA UGG CAU UUC UAG	Very strong skipping
182	H51D(+08-17)	AUC AUU UUU UCU CAU ACC UUC UGC U	No skipping
183	H51A/D(+08-17) & (-15+?)	AUC AUU UUU UCU CAU ACC UUC UGC UAG GAG CUA AAA	No skipping
184	H51A(+175+195)	CAC CCA CCA UCA GCC UCU GUG	No skipping
185	H51A(+199+220)	AUC AUC UCG UUG AUA UCC UCA A	No skipping

Table 37

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 52

Antisense oligonucleotides directed at exon 52 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 22 also shows differing efficiencies of four antisense molecules directed at exon 52 acceptor splice site. The most effective antisense oligonucleotide for inducing exon 52 skipping was H52A(+17+37) [SEQ ID NO:188).

Table 38 below shows antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 50 skipping. Antisense molecules H52A(+12+41) [SEQ ID NO:187] and

H52A(+17+37) [SEQ ID NO:188] showed the strongest exon 50 skipping at a concentration of 50 nM.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
186	H52A(-07+14)	UCC UGC AUU GUU GCC UGU AAG	No skipping
187	H52A(+12+41)	UCC AAC UGG GGA CGC CUC UGU UCC AAA UCC	Very strong skipping
188	H52A(+17+37)	ACU GGG GAC GCC UCU GUU CCA	Skipping to 50 nM
189	H52A(+93+112)	CCG UAA UGA UUG UUC UAG CC	No skipping
190	H52D(+05-15)	UGU UAA AAA ACU UAC UUC GA	No skipping

Table 38

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 53

Antisense oligonucleotides directed at exon 53 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 22 also shows antisense molecule H53A(+39+69) [SEQ ID NO:193] directed at exon 53 acceptor splice site. This antisense oligonucleotide was able to induce exon 53 skipping at 5, 100, 300 and 600 nM. A "cocktail" of three exon 53 antisense oligonucleotides: H53A(+23+47) [SEQ ID NO:195], H53A(+150+176) [SEQ ID NO:196] and H53D(+14-07) [SEQ ID NO:194], was also tested, as shown in Figure 20 and exhibited an ability to induce exon skipping.

Table 39 below includes other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 53 skipping. Antisense molecule H53A(+39+69) [SEQ ID NO:193] induced the strongest exon 53 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
191	H53A(+45+69)	CAU UCA ACU GUU GCC UCC GGU UCU G	Faint skipping at 50 nM
192	H53A(+39+62)	CUG UUG CCU CCG GUU CUG AAG GUG	Faint skipping at 50 nM
193	H53A(+39+69)	CAU UCA ACU GUU GCC UCC GGU UCU GAA GGU G	Strong skipping to 50 nM
194	H53D(+14-07)	UAC UAA CCU UGG UUU CUG UGA	Very faint skipping to 50 nM
195	H53A(+23+47)	CUG AAG GUG UUC UUG UAC UUC AUC C	Very faint skipping to 50 nM
196	H53A(+150+176)	UGU AUA GGG ACC CUC CUU CCA UGA CUC	Very faint skipping to 50 nM
197	H53D(+20-05)	CUA ACC UUG GUU UCU GUG AUU UUC U	Not made yet
198	H53D(+09-18)	GGU AUC UUU GAU ACU AAC CUU GGU UUC	Faint at 600 nM
199	H53A(-12+10)	AUU CUU UCA ACU AGA AUA AAA G	No skipping
200	H53A(-07+18)	GAU UCU GAA UUG UUU CAA CUA GAA U	No skipping
201	H53A(+07+26)	AUC CCA CUG AUU CUG AAU UC	No skipping
202	H53A(+124+145)	UUG GCU CUG GCC UGU CCU AAG A	No skipping

Table 39

What is claimed is:

1. A method for treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation of the DMD gene that is amenable to exon 53 skipping, comprising administering to the patient an antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

2. The method of claim 2, wherein the antisense oligonucleotide is administered intravenously.

ABSTRACT

An antisense molecule capable of binding to a selected target site to induce exon skipping in the dystrophin gene, as set forth in SEQ ID NO: 1 to 214.

FIGURE 1

bp Acceptor ESE Donor

uc$\boxed{\text{a}}$ugcacugaguga$\boxed{\text{ccucuuucucgcagG}}$CGCUAGC$\boxed{\text{UGGAG}}$CA/////CCGUGCAGACUGA$\boxed{\text{CGgucuca}}$u

SEQ ID NO:213

SEQ ID NO:214

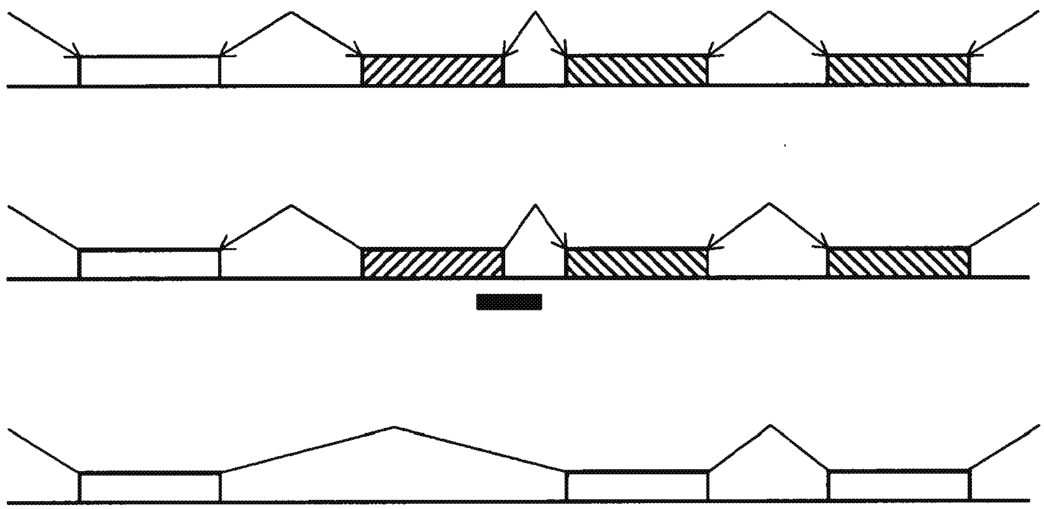


FIGURE 2

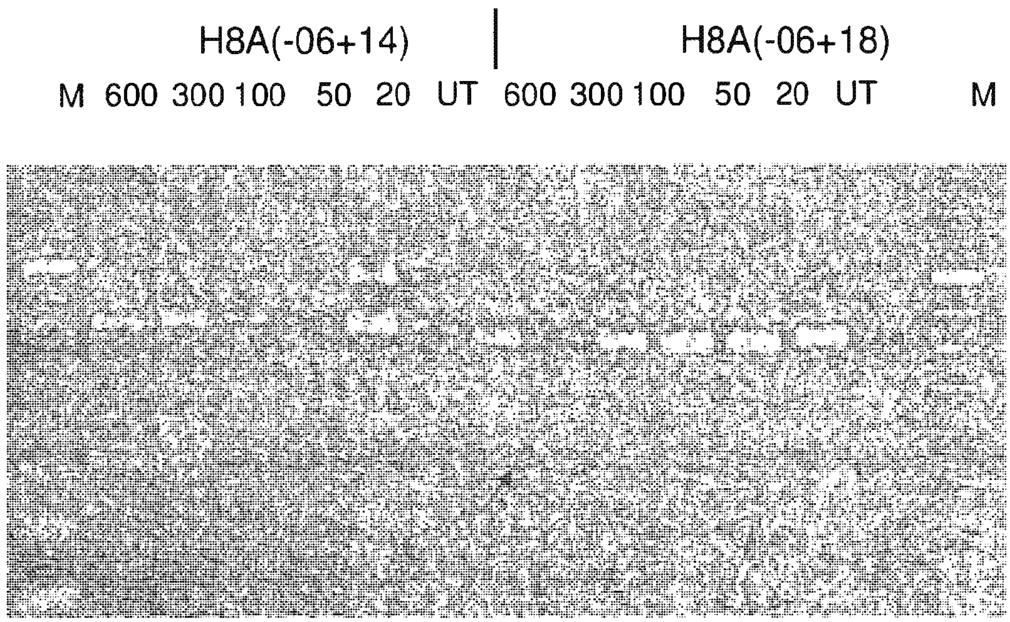


FIGURE 3

H7A(+45+67) H7A(+2+26)

M 600 300 100 50 20 600NM 600 300 100 50 20 600N M

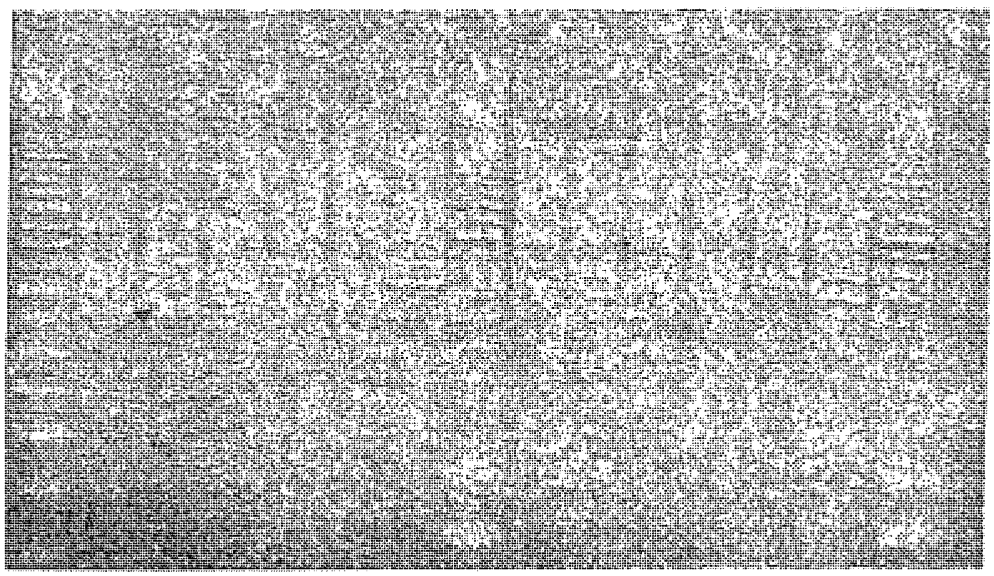


FIGURE 4

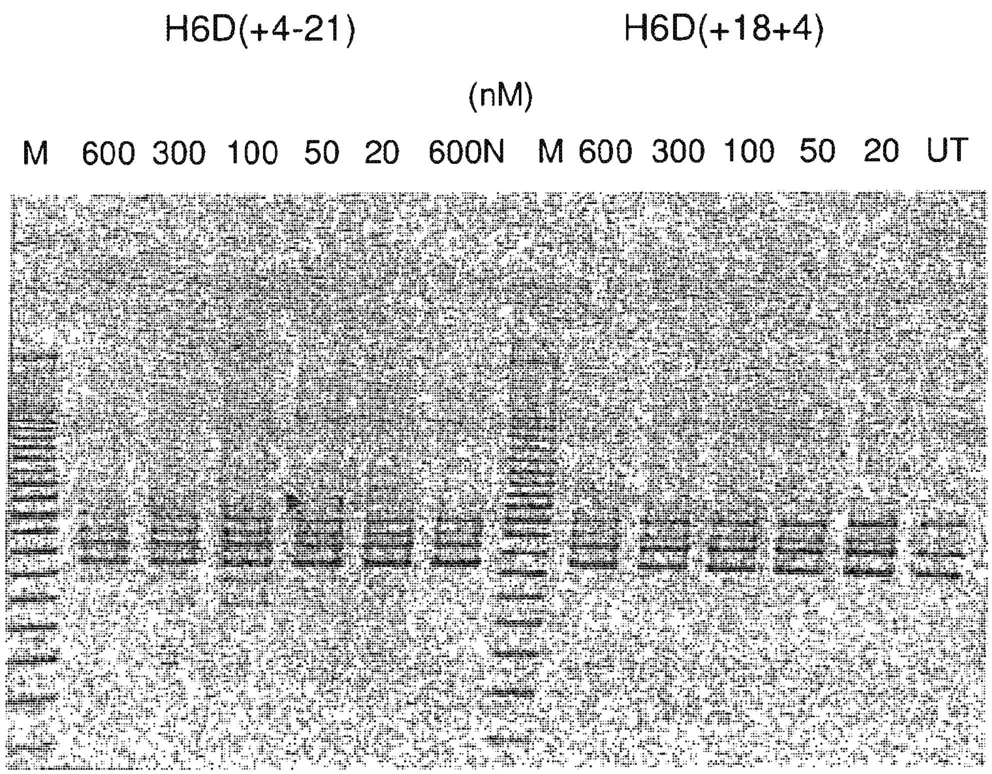


FIGURE 5

6A(+69+91)

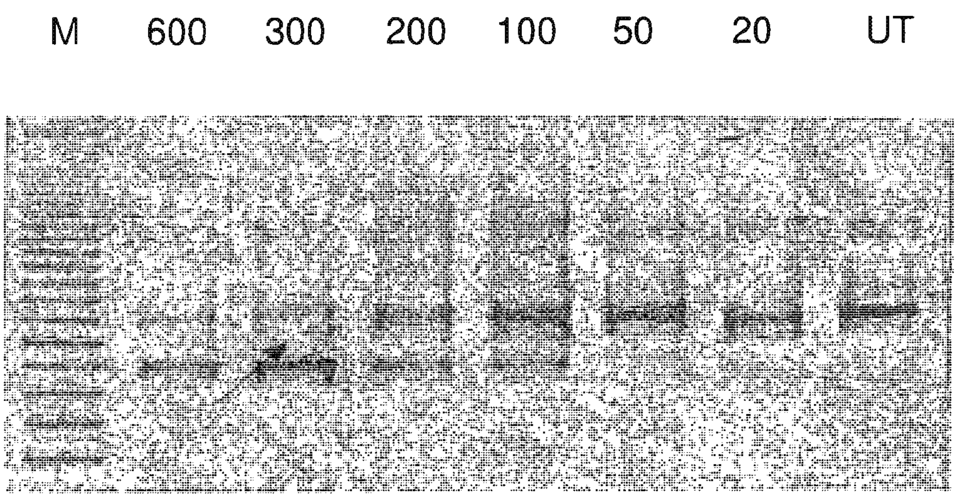


FIGURE 6

H4A(+13+32)

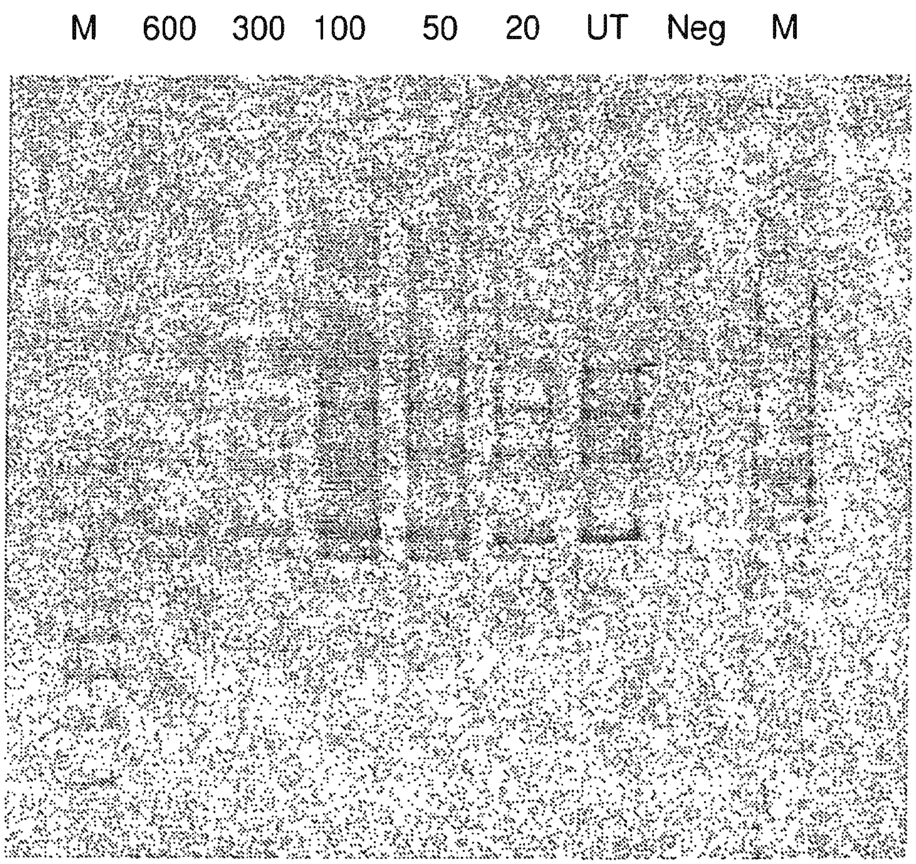
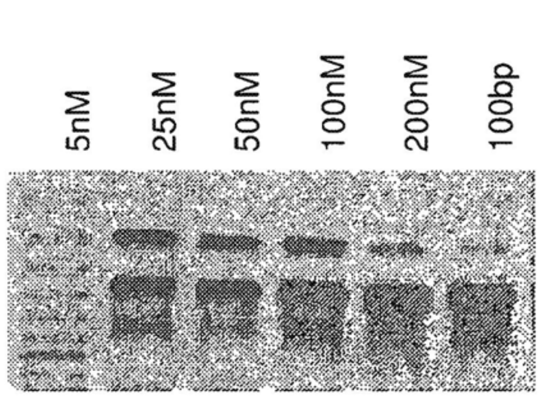
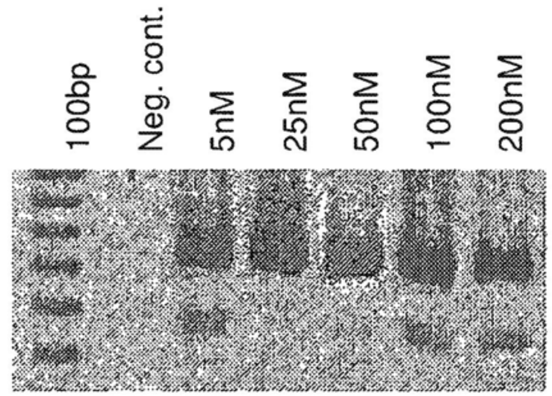


FIGURE 7



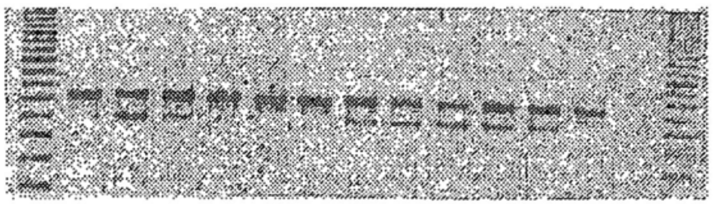
JSR610 - H12A(+52+75)

FIGURE 8A



JSR604 - H11A(+75+97)

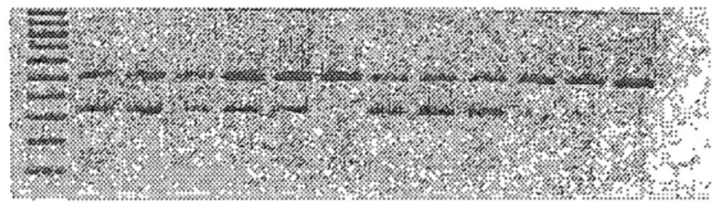
FIGURE 8B



H15A(+48+71) H15A(-12+19)

JSR428 JSR427

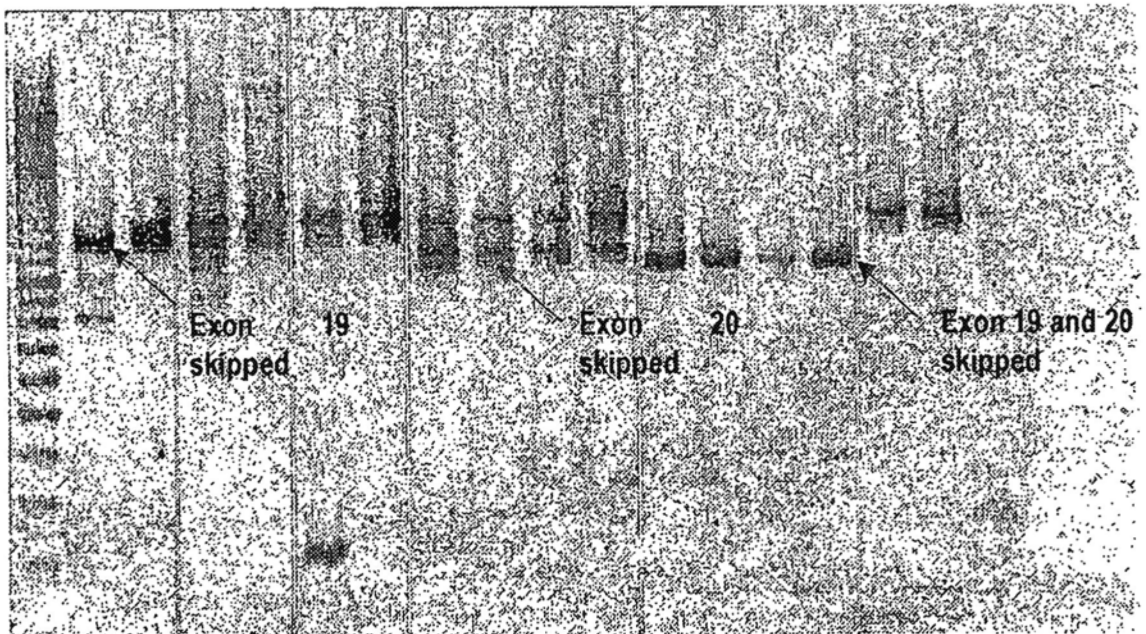
FIGURE 9A



H16A(-12+19) H16A(-06+25)

JSR390 JSR309

FIGURE 9B



100bp	600	100	600	100	600	100	600	300	100	50	600	300	100	50	L2K	UT
	HM19A(+35+36)		H20A(+44+71)		H20A(+149+170)		**20/20 cocktail** H20A(+44+71) H20A(+149+170)				**19/20/20 cocktail** HM19A(+35+36) H20A(+44+71) H20A(+149+170)					

FIGURE 10

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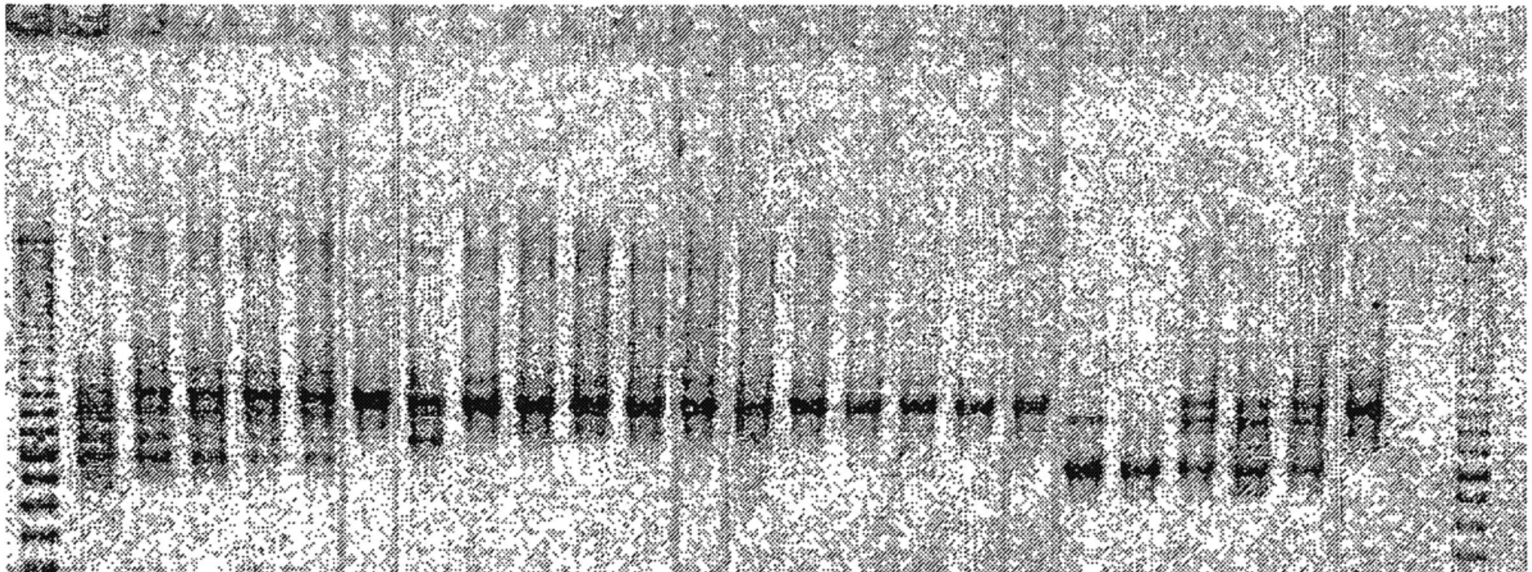
SRPT-VYDS-0006104



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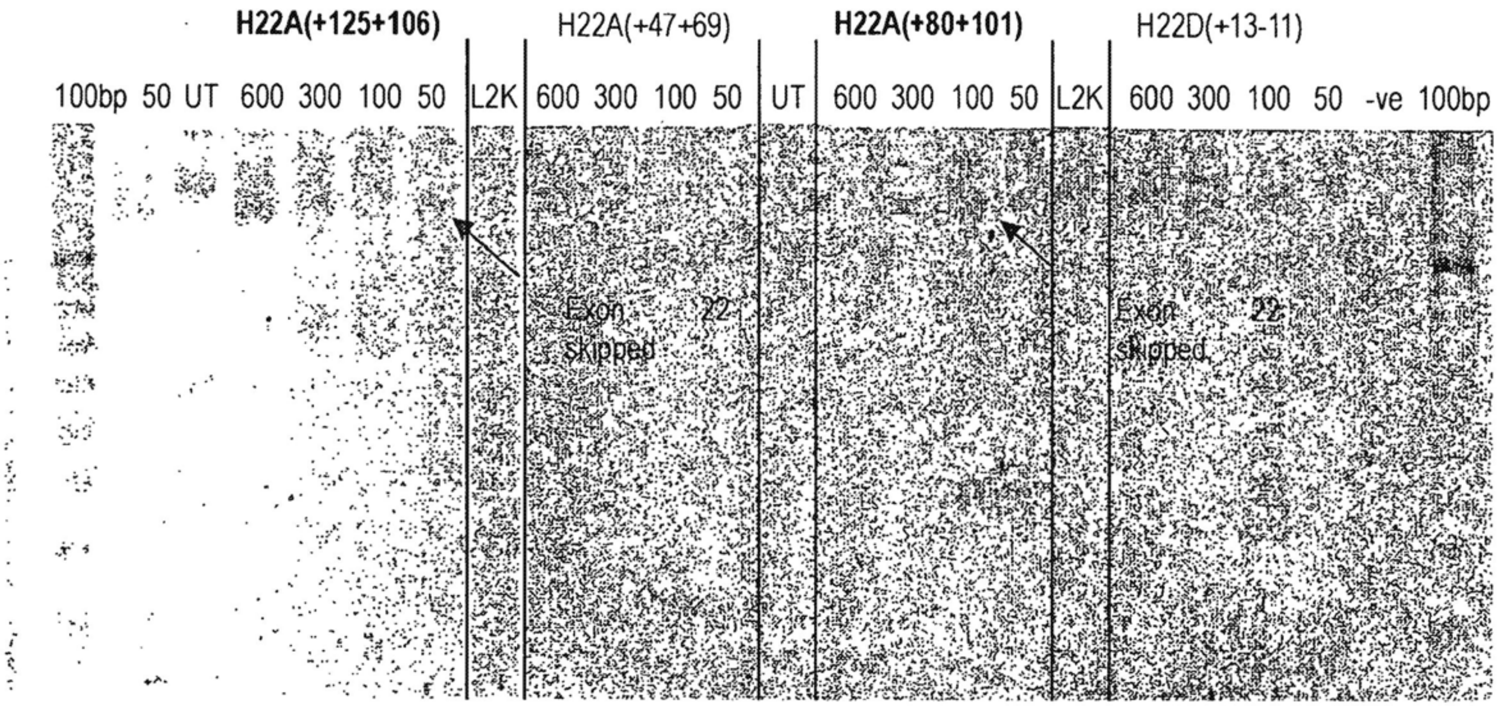
Weasel19/20/20	**Weasel19/20**	**Weasel19/20**	**19/20/20 cocktail**
H19A(+35+53)-aa- H20A(+44+63)-aa- H20A(+149+168)	H19A(+35+53)- aa- H20A(+44+63)	H19A(+35+53)- aa- H20A(+149+168)	HM19A(+35+36) H20A(+44+71) H20A(+149+170)

FIGURE 11



12/22

FIGURE 12

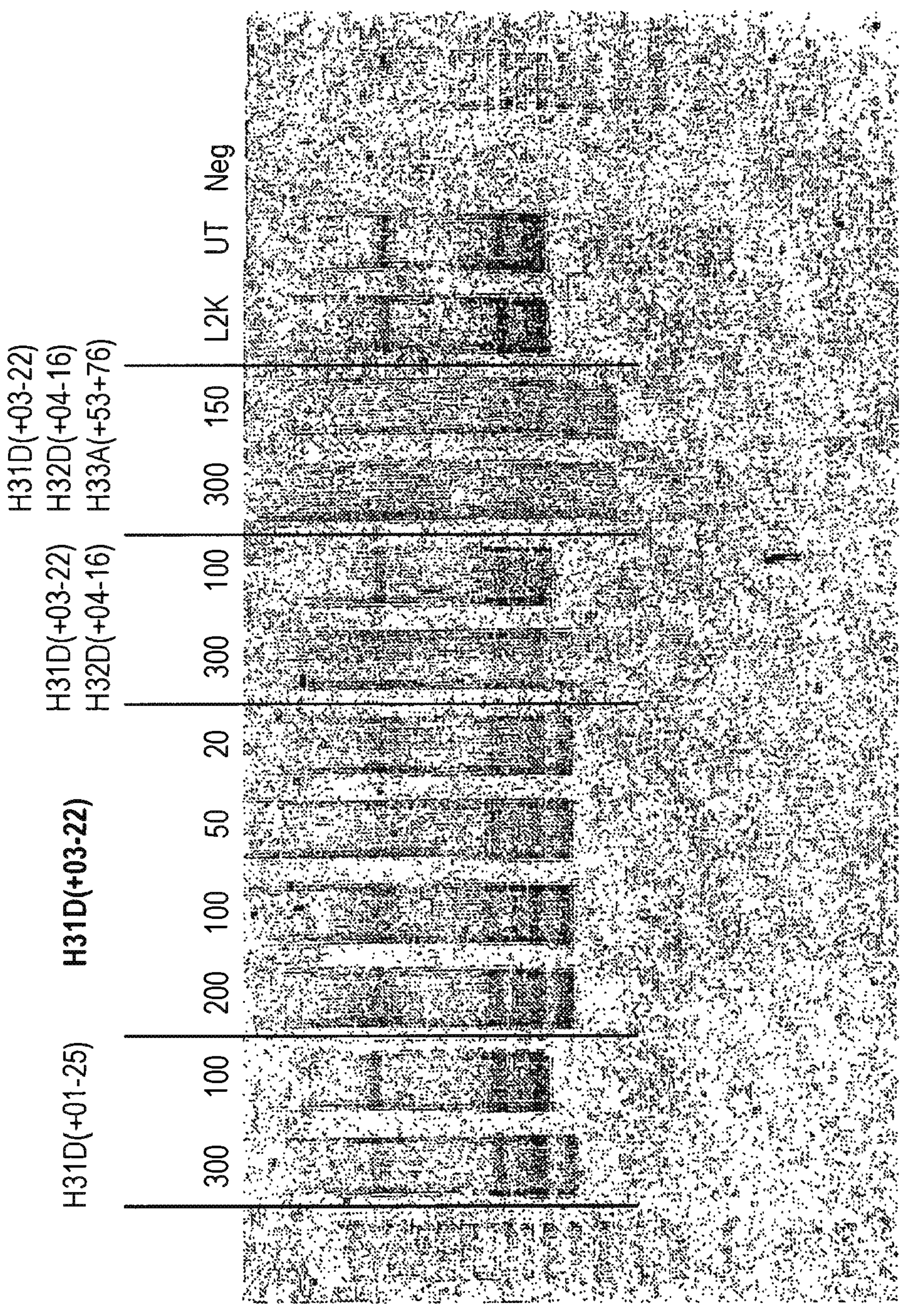

H31D(+01-25)
300
100
H31D(+03-22)
200
100
50
20
H31D(+03-22)
H32D(+04-16)
300
100
H31D(+03-22)
H32D(+04-16)
H33A(+53+76)
300
150
L2K
UT
Neg

FIGURE 13

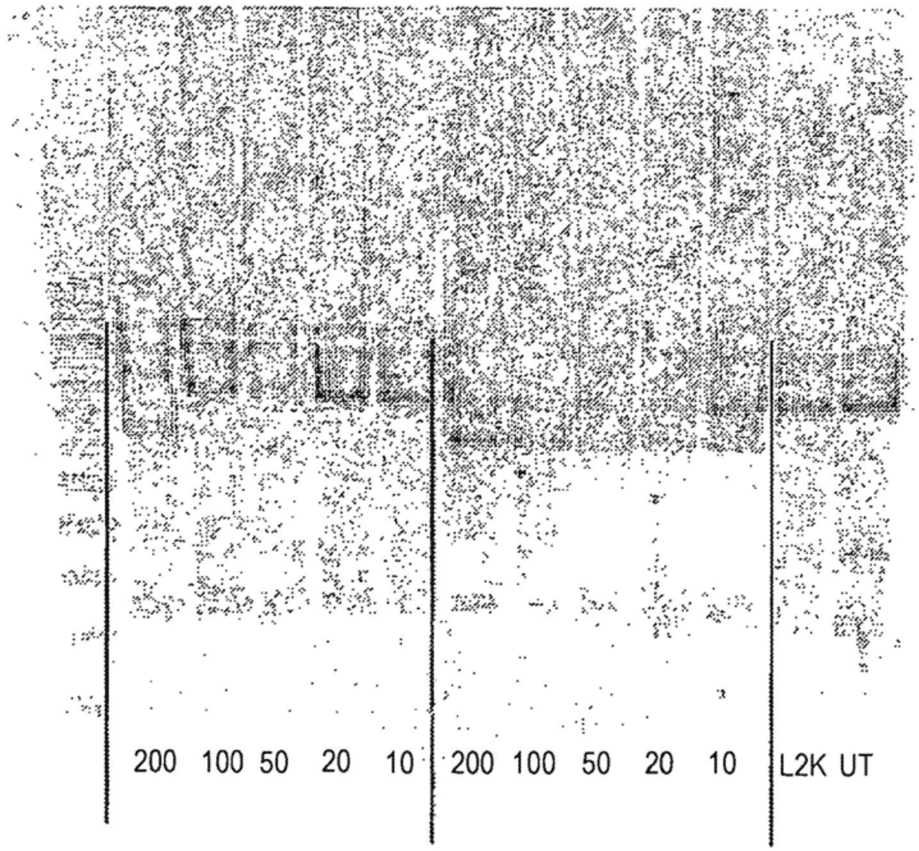
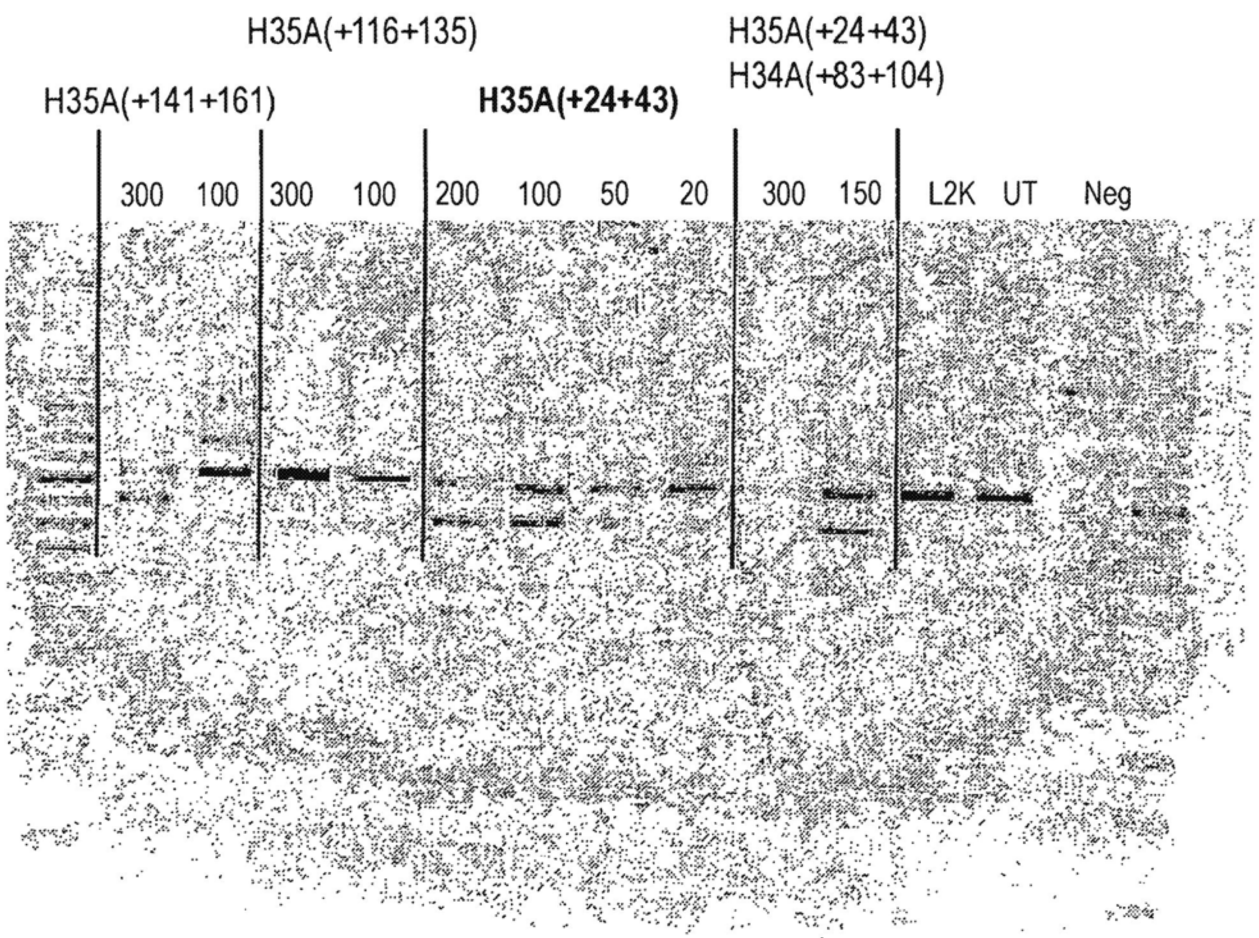


FIGURE 14



15/22

FIGURE 15

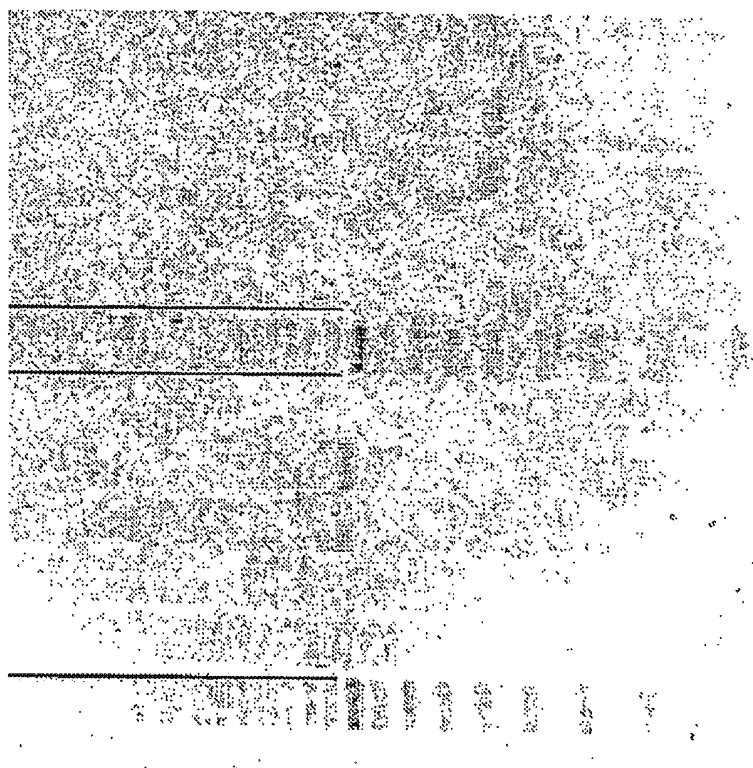


FIGURE 16

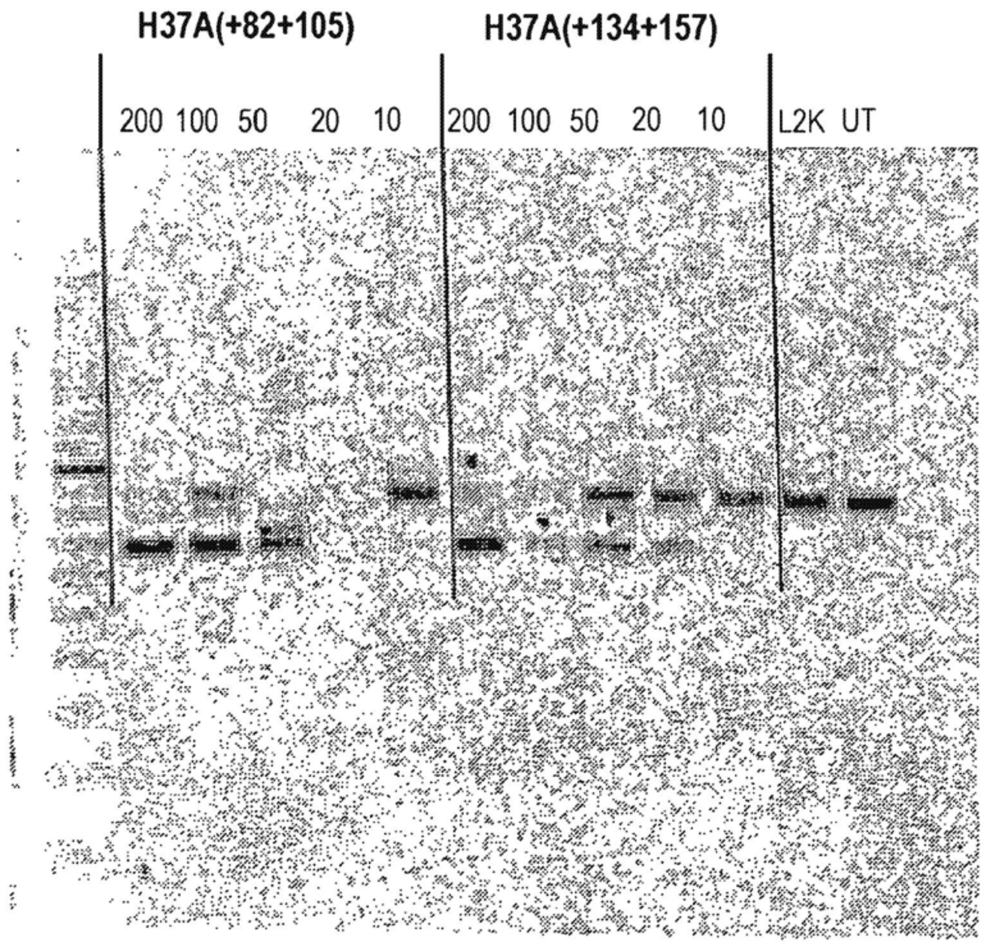


FIGURE 17

H38A(+88+112)

200 100 50 20 10 L2K UT

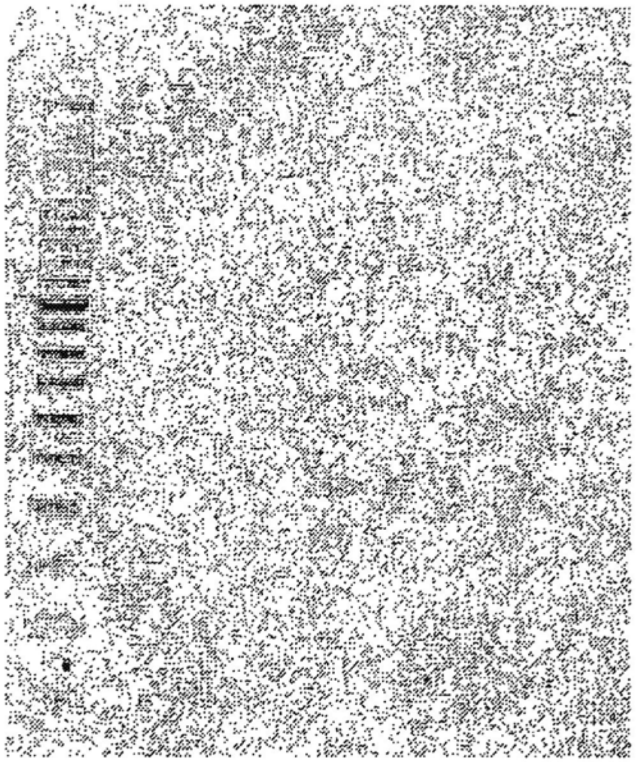


FIGURE 18

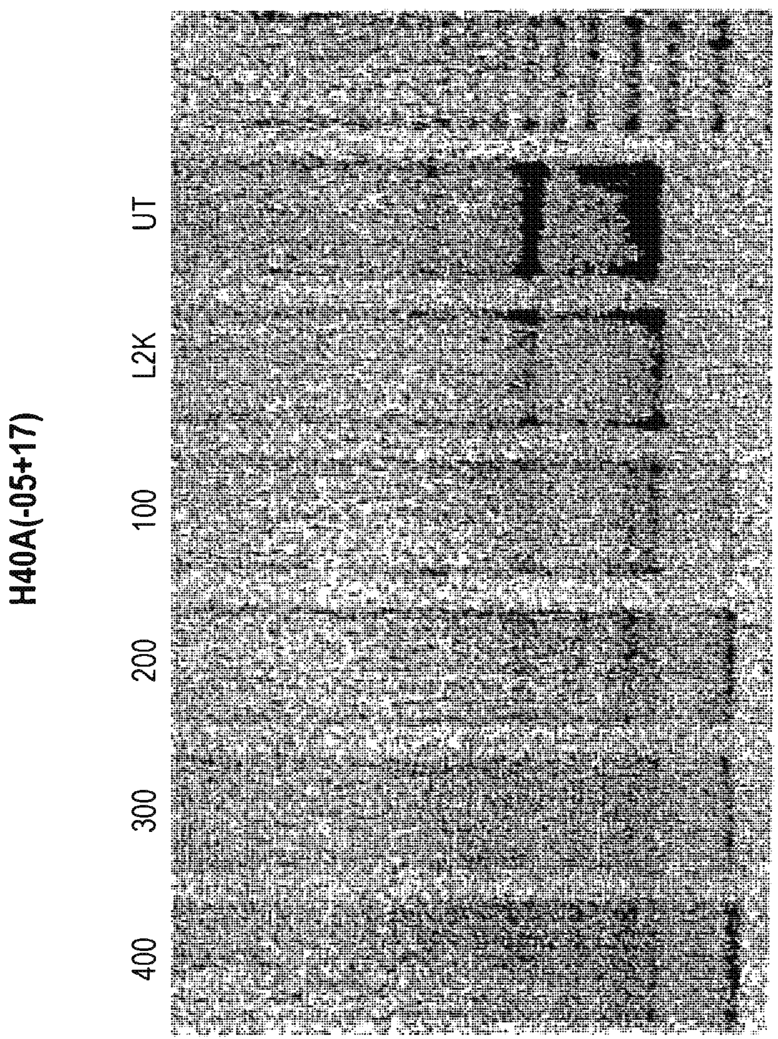


FIGURE 19

H42A(-4+23)

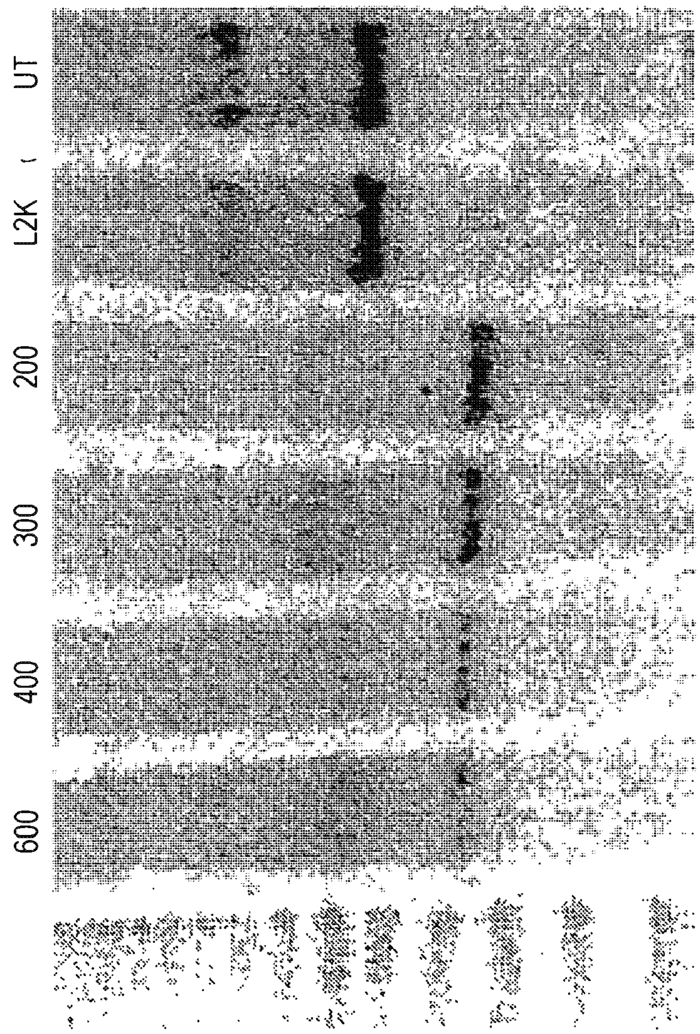


FIGURE 20

H46A(+86+115)

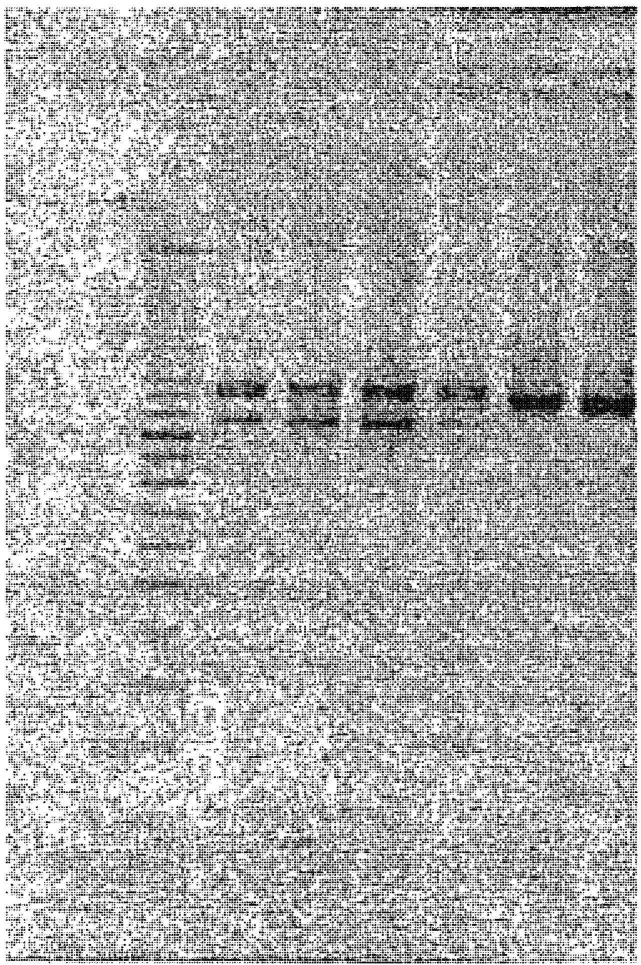
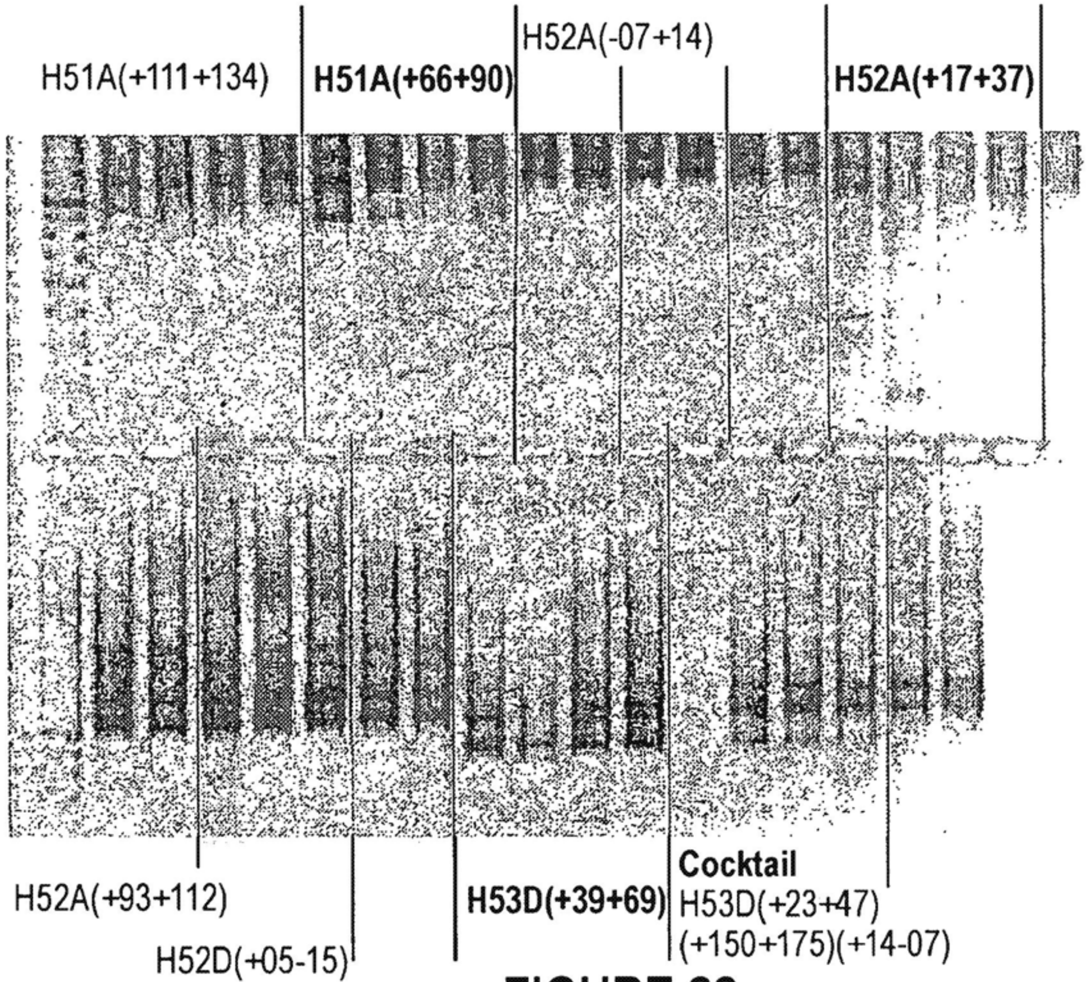


FIGURE 21



H51A(+111+134)
H51A(+66+90)
H52A(-07+14)
H52A(+17+37)
H52A(+93+112)
H52D(+05-15)
H53D(+39+69)
Cocktail
H53D(+23+47)
(+150+175)(+14-07)

FIGURE 22

4140_01500B1_SL_
SEQUENCE LISTING

<110> WILTON, STEPHEN DONALD
FLETCHER, SUE
MCCLOREY, GRAHAM

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<130> 4140.01500B1

<140> Not yet assigned
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<151> 2015-06-15

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<151> 2013-01-14

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<150> 12/837,359
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<151> 2008-01-15

<150> PCT/AU2005/000943
<151> 2005-06-28

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Human 2'-O-methyl phosphorothioate antisense
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oligonucleotide

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Human 2'-O-methyl phosphorothioate antisense
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<210> 82
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<210> 83
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<210> 87
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<212> RNA
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<210> 89
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oligonucleotide

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oligonucleotide

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Human 2'-O-methyl phosphorothioate antisense
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Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Filer:	John Michael Covert/Tamara Haynesworth
Attorney Docket Number:	4140.01500B1

Filed as Small Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	75	75
UTILITY SEARCH FEE	2111	1	330	330
UTILITY EXAMINATION FEE	2311	1	380	380
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		2855

Electronic Acknowledgement Receipt

EFS ID:	33537848
Application Number:	16112453
International Application Number:	
Confirmation Number:	3144
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	153767
Filer:	John Michael Covert/Tamara Haynesworth
Filer Authorized By:	John Michael Covert
Attorney Docket Number:	4140.01500B1
Receipt Date:	24-AUG-2018
Filing Date:	
Time Stamp:	18:45:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$2855
RAM confirmation Number	082718INTEFSW18474600
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	2018-08-24-Miscellaneous-Letter-4140-01500B1.PDF	280522 50bf66960b809c2facbb810d3cb2400164844765	no	2
Warnings:					
Information:					
2	Transmittal of New Application	2018-08-24-Utility-Transmittal-4140-01500B1.pdf	213018 91f9d9495a2b7c48155668ea30e8ca9b0124f2f9	no	2
Warnings:					
Information:					
3	TrackOne Request	2018-08-24-Request-TrackOne-4140-01500B1.PDF	249409 dc813ef3cafa8484402ef04f4dca1c58b7061b36	no	2
Warnings:					
Information:					
4	Authorization for Extension of Time all replies	2018-08-24-EOT-Authorization-4140-01500B1.PDF	116474 1ca0ce2a5962032ea04d6c2ddc29f7140fdf409c	no	1
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Information:					
5	Application Data Sheet	2018-08-24-ADS-4140-01500B1.PDF	109399 b6bec3f720473f003336a4d29f9aeeba97147a7e	no	9
Warnings:					
Information:					
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6		2018-08-24-Nonprovisional-Application-4140-01500B1.PDF	261912 7b9b0fe5be13193ca8d2a1e4af24e0faa10859de	yes	68

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	66	
	Claims		67	67	
	Abstract		68	68	
Warnings:					
Information:					
7	Drawings-only black and white line drawings	2018-08-24-Drawing-4140-01500B1.pdf	2081956 1b8f210117197c7bee661bdb39bbce54b746ebfa	no	22
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Information:					
8	Sequence Listing (Text File)	4140_01500B1_SL_.txt	62078	no	-
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9	Fee Worksheet (SB06)	fee-info.pdf	38505 e6704b4eee8cddd9f6a1c1a39adcb286fc1f36b0	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3413273		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

JOHN M. COVERT
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Sterne Kessler
STERNE KESSLER GOLDSTEIN & FOX

August 24, 2018

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Re: U.S. Non-Provisional Utility Patent Application Under 37 C.F.R. § 1.53(b)
(*Continuation of Appl. No. 15/274,772; Filing Date: September 23, 2016*)
Appl. No. *To Be Assigned*; Filing Date: August 24, 2018
For: **ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF**
Applicant: The University of Western Australia
Our Ref: 4140.01500B1

Commissioner:

Transmitted herewith for appropriate action are the following documents:

1. Payment made via EFS-Web in the amount of $2,855.00 (small entity) to cover:

$2,000.00	Track 1 Filing Fee – Certification and Request for Prioritized Examination (Track 1);
$70.00	Processing Fee - Certification and Request for Prioritized Examination (Track 1);
$785.00	Patent Application Fee (including basic filing, search, and examination fees);

2. Utility Patent Application Transmittal (PTO/AIA/15);

3. Certification and Request for Prioritized Examination Under 37 C.F.R. § 1.102(e) (Track 1);

4. Authorization to Treat a Reply As Incorporating An Extension of Time Under 37 C.F.R. § 1.136(a)(3);

5. U.S. Utility Patent Application entitled:

   ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

   and naming as inventors:

   Stephen Donald WILTON, Sue FLETCHER, and Graham MCCLOREY

the application containing:

i. 66 pages of description prior to the claims;

ii. 1 page of claims (2 claims);

iii. a one (1) page abstract;

iv. 22 sheets of drawings: (Figures 1-22);

6. An Application Data Sheet (37 C.F.R. § 1.76);

7. Sequence Listing (text file).

The above-listed documents are filed electronically through EFS-Web.

Correspondence should be sent to Customer No. 153767.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency and any additional fees required to continue prosecution or appeal of this application (including issue fee, fees for net addition of claims or forwarding to appeal) or credit any overpayment to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

John M. Covert

John M. Covert
Attorney for Applicant
Registration No. 38,759

JMC/NPS:dmc
Enclosures

9891263_1.docx

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [ ] The attached application, or
- [x] United States application or PCT international application number 13/741,150 filed on 01/14/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Stephen Donald WILTON Date (Optional): 26/03/13

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

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LEGAL NAME OF INVENTOR

Inventor: Sue FLETCHER Date (Optional): 26/03/2013

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

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☐ The attached application, or

☒ United States application or PCT international application number 13/741,150 filed on 01/14/2013 .

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LEGAL NAME OF INVENTOR

Inventor: Graham MCCLOREY Date (Optional): 26-03-13

Signature: Graham McClorey

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Electronic Patent Application Fee Transmittal

Application Number:	16112453
Filing Date:	24-Aug-2018
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Filer:	Neil P. Shull/Debbie Colonna
Attorney Docket Number:	4140.01500B1

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	2051	1	80	80
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		80

Electronic Acknowledgement Receipt

EFS ID:	34311459
Application Number:	16112453
International Application Number:	
Confirmation Number:	3144
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	153767
Filer:	Neil P. Shull/Debbie Colonna
Filer Authorized By:	Neil P. Shull
Attorney Docket Number:	4140.01500B1
Receipt Date:	14-NOV-2018
Filing Date:	24-AUG-2018
Time Stamp:	16:49:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$80
RAM confirmation Number	111518INTEFSW16495600
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	2018-11-14-Response-Notice-File-Corr-App-Papers-4140-01500B1.PDF	107139 f0c34b6cd12377c0906472ccf4f334b2003bcccd	no	3
Warnings:					
Information:					
2	Drawings-only black and white line drawings	2018-11-14-Replacement-Drawings-4140-01500B1.PDF	13179958 491d61cbdfb902ccf76a8a20a11fd6622357e6f7	no	22
Warnings:					
Information:					
3	Oath or Declaration filed	2018-11-14-Declarations-4140-01500B1.PDF	291510 c6e328c39fa4ec45ebad1b5748dffa8d3d35739f	no	3
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30666 0c4b4f850d518ffcbde5a721bfe45b8402bf2ccb	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	13609273		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

8319.53.45T1

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 01/31/2018. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
16/112,453	August 24, 2018

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 153767

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number: 153767

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

THE UNIVERSITY OF WESTERN AUSTRALIA

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Robyn Owens	Date (Optional)	- 6 DEC 2018
Name	Professor Robyn Owens		
Title	Deputy Vice-Chancellor (Research)		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: The University of Western Australia

Application No./Patent No.: 16/112,453 Filed/Issue Date: August 24, 2018

Titled: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

The University of Western Australia, a university

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

☐ The extent (by percentage) of its ownership interest is ______________%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 047727, Frame 0025, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: ______________________ To: ______________________

The document was recorded in the United States Patent and Trademark Office at

Reel ______________, Frame ______________, or for which a copy thereof is attached.

2. From: ______________________ To: ______________________

The document was recorded in the United States Patent and Trademark Office at

Reel ______________, Frame ______________, or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: ______________________________ To: ______________________________

The document was recorded in the United States Patent and Trademark Office at

Reel ____________, Frame ____________, or for which a copy thereof is attached.

4. From: ______________________________ To: ______________________________

The document was recorded in the United States Patent and Trademark Office at

Reel ____________, Frame ____________, or for which a copy thereof is attached.

5. From: ______________________________ To: ______________________________

The document was recorded in the United States Patent and Trademark Office at

Reel ____________, Frame ____________, or for which a copy thereof is attached.

6. From: ______________________________ To: ______________________________

The document was recorded in the United States Patent and Trademark Office at

Reel ____________, Frame ____________, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/John M. Covert/ John M. Covert Reg. #38,759 for	13 Dec. 2018
Signature	Date
Eric K. Steffe	36,688
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	34574407
Application Number:	16112453
International Application Number:	
Confirmation Number:	3144
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	153767
Filer:	Neil P. Shull/Debbie Colonna
Filer Authorized By:	Neil P. Shull
Attorney Docket Number:	4140.01500B1
Receipt Date:	13-DEC-2018
Filing Date:	24-AUG-2018
Time Stamp:	13:49:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	4140_01500B1_POA.pdf	2016918 ff818c0fcd497169f69d84203620303a98a2c cc0	no	1

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	4140_01500B1_Statement_373c.pdf	81696 e91e953a715aa237407a3de288571fda70638083	no	3
Warnings:					
Information:					
		Total Files Size (in bytes):	2098614		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/112,453	08/24/2018	Stephen Donald WILTON	4140.01500B1

CONFIRMATION NO. 3144

POA ACCEPTANCE LETTER

153767
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

OC000000104521137

Date Mailed: 12/18/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/13/2018.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/tlulu/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: WILTON, S., et al.	Confirmation No.: 3144
Applicant: SAREPTA THERAPEUTICS	Art Unit: 1635
Application No.: 16/112,453	Examiner: CHONG, K.
Filing Date: August 24, 2018	Atty. Docket: 4140.01500B1

Title: **ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF**

Information Disclosure Statement

Mail Stop Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

Listed on accompanying IDS Forms PTO/SB/08a/b equivalent are documents that may be considered material to the patentability of this application as defined in 37 C.F.R. §1.56, and in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.97 and 1.98.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicant has listed publication dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

Applicant has checked the appropriate boxes below.

☐ 1. Statement under 37 C.F.R. 1.704(d). Each item of information contained in this Information Disclosure Statement: (i) was first cited in any communication from a patent office in a counterpart[1] foreign or international application or from the Office; and this communication was not received by any individual designated in Sec. 1.56(c) more than thirty days prior to the filing of this information disclosure statement; OR (ii) is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in Sec. 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ 2. Filing under 37 C.F.R. § 1.97(b). This Information Disclosure Statement is being filed within three months of the date of filing of a national application other than a continued prosecution application (CPA), OR within three months of the date of entry of the national stage as set forth in 37 C.F.R. § 1.491 in an international application, OR before the mailing date of a first Office Action on the merits OR before the mailing of a first Office Action

[1] The term counterpart foreign patent application means that a claim for priority has been made in either the U.S. application or a foreign application based on the other, or that the disclosures of the U.S. and foreign patent applications are substantively identical (e.g., an application filed in the European Patent Office claiming the same U.K. priority as claimed in the U.S. application).

after the filing of a request for continued examination under 37 C.F.R. § 1.114. No statement or fee is required.

☒ 3. Filing under 37 C.F.R. § 1.97(c). This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection, or Notice of Allowance, or an action that otherwise closes prosecution in the application.

☐ a. Statement under 37 C.F.R. § 1.97(e)(1). I hereby state that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. Statement under 37 C.F.R. § 1.97(e)(2). I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☒ c. The required fee is provided through online credit card payment authorization in the amount of $120.00 in payment of the fee under 37 C.F.R. § 1.17(p).

☐ 4. Filing under 37 C.F.R. § 1.97(d) This Information Disclosure Statement is being filed more than three months after the U.S. filing date and after the mailing date of a Final Rejection or

Notice of Allowance, but on or before payment of the Issue Fee. The required fee is provided through online credit card payment authorization in the amount of $120.00 in payment of the fee under 37 C.F.R. § 1.17(p); in addition:

☐ a. Statement under 37 C.F.R. § 1.97(e)(1). I hereby state that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. Statement under 37 C.F.R. § 1.97(e)(2). I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ 5. The patent family for one or more foreign language documents submitted herewith includes a United States patent, and other patent, in the English language. Copies of both the particular foreign patent(s) or published foreign patent applications cited in the foreign patent office communication, and that are not already of record in this application, are enclosed. Copies of the related United States or other English language patent or published application from the family list, if not already of record, are listed on the accompanying SB/08A form. For the purposes of a statement under 37 CFR 1.97(e)(1), the United States or

other English language patent or published application are to be construed as being cited by the foreign patent office. MPEP 609.04(b)(V).

☐ 6. The document(s) was/were cited in a search report by a foreign patent office in a counterpart foreign application. Submission of an English language version of the search report that indicates the degree of relevance found by the foreign office is provided in satisfaction of the requirement for a concise explanation of relevance. MPEP 609.04(a)(III).

☐ 7. A concise explanation of the relevance of the non-English language document(s) appears below in accordance with 37 C.F.R. § 1.98(a)(3).

☒ 8. Copies of documents **NPL709-NPL714** are submitted. However, copies of documents **FP1-FP127** and **NPL1-NPL708** are not submitted. In addition, in accordance with 37 C.F.R. § 1.98(a)(2)(ii), no copies of U.S. patents and patent application publications cited as documents **US1-US219** on the attached IDS Forms are submitted.

☒ 9. Copies of the **FP1-FP127** and **NPL1-NPL708** documents were cited by or submitted to the Office in an IDS that complies with 37 C.F.R. § 1.98(a)-(c) in Application No. 15/274,772, filed September 23, 2016, which is relied upon for an earlier filing date under 35 U.S.C. § 120. Thus, copies of these documents are not attached. 37 C.F.R. § 1.98(d).

☐ 10. It is expected that the examiner will review the prosecution and cited art in the parent Application No(s). ______________________ in accordance with MPEP 2001.06(b), and indicate in the next communication from the office that the art cited in the earlier prosecution history has been reviewed in connection with the present application.

☒ 11. In accordance with the Federal Circuit decision in *Dayco Prods., Inc. v. Total Containment, Inc.* 329 F.3d 1358 (Fed. Cir. 2003), Applicant submits herewith Office Actions from the co-pending U.S. Patent Application No. 15/645,842, filed July 10, 2017, as document **NPL709**; U.S. Patent Application No. 15/655,646, filed July 20, 2017, as documents **NPL710**; U.S. Patent Application No. 15/673,019, filed August 9, 2017, as document **NPL711;** and U.S. Patent Application No. 16/112,371, filed August 24, 2018, as document **NPL714**. The identification of these Office Actions is not to be construed as a waiver of secrecy as to those applications now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination.

It is respectfully requested that the Examiner initial and return a copy of the enclosed IDS Forms, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/Neil P. Shull/

Neil P. Shull
Attorney for Applicant
Registration No. 60,238

Date: __January 17, 2019_____

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
10582165_1.docx

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	16/112,453
	Filing Date	August 24, 2018
	First Named Inventor	WILTON, Stephen
	Art Unit	1635
	Examiner Name	K. Chong
	Attorney Docket Number	4140.01500B1

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	16/112,453
	Filing Date	August 24, 2018
	First Named Inventor	WILTON, Stephen
	Art Unit	1635
	Examiner Name	K. Chong
	Attorney Docket Number	4140.01500B1

	NPL1	Extended European Search Report, EP 17159328.8, dated September 5, 2017, 10 pages.

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Attorney Docket Number	4140.01500B1

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Examiner Initial*	Cite No	Patent Number	Kind Code1	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	US1	9506058		2016-11-29	Kaye	
	US2	9605262		2017-03-28	Wilton et al.	

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	US3	20130190390	A1	2013-07-25	SAZANI et al.	
	US4	20170009233	A1	2017-01-12	WILTON et al.	

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	FP1	2013/142087	WO	A1	2013-09-26	Sarepta Therapeutics, Inc		

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	Art Unit	1635
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	FP2	2014/172669	WO	A1	2014-10-23	Research Institute at Nationwide Children's Hosp.		
	FP3	2017/059131	WO	A1	2017-04-06	Sarepta Therapeutics, Inc		

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	NPL2	GenBank AF213437.1 Dated January 17, 2002	
	NPL3	International Search Report and Written Opinion, PCT/US2016/054534, dated January 17, 2017, 13 pages.	
	NPL4	KOLE et al., "Exon skipping therapy for Duchenne muscular dystrophy," Advanced Drug Delivery Reviews, vol. 87:104-107 (2015).	
	NPL5	WHO Drug Information, International Nonproprietary Names for Pharmaceutical Substances (INN), Proposed INN: List 115, "CASIMERSEN," vol. 30(2): 3 pages (2016)	
	NPL6	WHO Drug Information, International Nonproprietary Names for Pharmaceutical Substances (INN), Proposed INN: List 115, "Golodirsen," vol. 30(2): 3 pages (2016)	

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	US5	8436163		2013-05-07	Iversen et al.	
	US6	9416361		2016-08-16	Iversen et al.	

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	US7	20040266720	A1	2004-12-30	Iversen et al.	
	US8	20120053228	A1	2012-03-01	Iversen et al.	
	US9	20140045916	A1	2014-02-13	Iversen et al.	
	US10	20150232839	A1	2015-08-20	Iversen et al.	

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	US11	20160298111	A1	2016-10-13	Bestwick et al.	

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	US12	9453225		2016-09-27	Sazani et al.	
	US13	9447417		2016-09-20	Sazani et al.	
	US14	9447416		2016-09-20	Sazani et al.	
	US15	9447415		2016-09-20	Wilton et al.	
	US16	9441229		2016-09-13	Wilton et al.	
	US17	9434948		2016-09-06	Sazani et al.	
	US18	9422555		2016-08-23	Wilton et al.	

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	US19	20160177301	A1	2016-06-23	Wilton et al.	

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	NPL7	Errata to the Sarepta Briefing Information for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Eteplirsen Errata Document, NDA 206488, 5 pages.	
	NPL8	Extended European Search Report, EP 15190341.6, dated April 28, 2016, 9 pages.	
	NPL9	FDA Briefing Information for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Eteplirsen, NDA 206488, 115 pages	
	NPL10	FDA News Release, "FDA grants accelerated approval to first drug for Duchenne muscular dystrophy," September 19, 2016, 3 pages.	

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	Attorney Docket Number	4140.01500B1

	NPL11	Jett Foundation Presentation by McSherry, C. "Patient and Caregiver-Reported Outcomes of Patients in Clinical Trials of Eteplirsen for Treatment of Duchenne" at Peripheral and Central Nervous System Drugs Advisory Committee, April 25, 2016, 17 pages.	
	NPL12	Letter from the FDA to Sarepta Therapeutics, Inc., Re: ACCELERATED APPROVAL for the use of Exondys 51 (eteplirsen), FDA Reference ID: 3987286, dated September 19, 2016, 11 pages.	
	NPL13	Letter to the U.S. Food and Drug Administration, (Dr. Billy Dunn, M.D. Director Division of Neurology Products, Office of Drug Evaluation 1, Center for Drug Evaluation and Research), for The Peripheral and Central Nervous System Advisory Committee Meeting (AdComm) supporting approval of eteplirsen, dated February 24, 2016, 4 pages.	
	NPL14	Letter to the U.S. Food and Drug Administration, (Dr. Janet Woodcock, M.D. Director, CDER), from The Congress of The United States regarding Duchenne muscular dystrophy, dated February 17, 2016, 7 pages.	
	NPL15	Prescribing Information for EXONDYS 51 (eteplirsen) Injection, dated 09/2016, 10 pages	
	NPL16	Sarepta Briefing Information for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Eteplirsen Briefing Document, NDA 206488, 186 pages.	
	NPL17	Sarepta Presentation at Peripheral and Central Nervous System Drugs Advisory Committee, April 25, 2016, 133 pages	
	NPL18	Sarepta Press Release, Sarepta Issues Statement on Advisory Committee Outcome for Use of Eteplirsen in the Treatment of Duchenne Muscular Dystrophy, April 25, 2016, 2 pages	
	NPL19	Sarepta Therapeutics, Inc. News Release, "Sarepta Therapeutics Announces FDA Accelerated Approval of EXONDYS 51™ (eteplirsen) injection, an Exon Skipping Therapy to Treat Duchenne Muscular Dystrophy (DMD) Patients Amenable to Skipping Exon 51," September 19, 2016, 2 pages.	
	NPL20	U.S. Food and Drug Administration Presentation at Peripheral and Central Nervous System Drugs Advisory Committee, April 25, 2016, 178 pages.	
	NPL21	University of Western Australia v. Academisch Ziekenhuis Leiden, Decision - Motions - 37 C.F.R. § 41.125(a), filed in Patent Interference No. 106008, September 20, 2016, pages 1-20 (Doc 480)	

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Attorney Docket Number	4140.01500B1

	NPL22	University of Western Australia v. Academisch Ziekenhuis Leiden, Decision - Motions - 37 CFR § 41.125(a) (Substitute), filed in Patent Interference No. 106007, May 12, 2016, pages 1-53 (Doc 476)	
	NPL23	University of Western Australia v. Academisch Ziekenhuis Leiden, Judgment - Motions - 37 C.F.R. § 41.127 filed in Patent Interference No. 106008, September 20, 2016, pages 1-3 (Doc 481)	
	NPL24	University of Western Australia v. Academisch Ziekenhuis Leiden, Judgment - Motions - 37 CFR § 41.127, filed in Patent Interference No. 106007, April 29, 2016, pages 1-3, (Doc 474)	
	NPL25	University of Western Australia v. Academisch Ziekenhuis Leiden, Redeclaration - 37 CFR 41.203(c), filed in Patent Interference No. 106007, April 29, 2016, pages 1-2, (Doc 473)	
	NPL26	University of Western Australia v. Academisch Ziekenhuis Leiden, Withdrawal and Reissue of Decision on Motions, filed in Patent Interference No. 106007, May 12, 2016, pages 1-2 (Doc 475)	
	NPL27	University of Western Australia v. Academisch Ziekenhuis Leiden, Decision - Motions - 37 CFR § 41.125(a), filed in Patent Interference No. 106007, April 29, 2016, pages 1-53, (Doc 472)	

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	FP4	2000-325085	JP	A	2000-11-28	MATSUO MASAFUMI, ET AL.		
	FP5	2002-010790	JP	A	2002-01-15	MATSUO MASAFUMI, ET AL.		
	FP6	2002-325582	JP	A	2002-11-12	MATSUO, MASAFUMI, ET AL.		

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	Attorney Docket Number	4140.01500B1

	FP7	2002-340857	JP	A	2002-11-27	MATSUSHITA ELECTRIC IND CO LTD		
	FP8	2002-529499	JP	A	2002-09-10	ELI LILLY AND COMPANY		
	FP9	2004-509622	JP	A	2004-04-02	ACADEMISCH ZIEKENHUIS LEIDEN		
	FP10	2010-268815	JP	A	2010-12-02	MATSUO MASAFUMI		
	FP11	2011-101655	JP	A	2011-05-26	ACADEMISCH ZIEKENHUIS LEIDEN		
	FP12	2011-200235	JP	A	2011-10-13	ACADEMISCH ZIEKENHUIS LEIDEN		
	FP13	2014-054250	JP	A	2014-03-27	NIPPON SHINYAKU CO LTD.		
	FP14	2014-111638	JP	A	2014-06-19	ACADEMISCH, ZIEKENHUIS LEIDEN		
	FP15	2014-138589	JP	A	2014-07-31	ACADEMISCH, ZIEKENHUIS LEIDEN		
	FP16	4777777	JP	B2	2011-09-21	KOBE UNIVERSITY		
	FP17	4846965	JP	B2	2011-12-28	ACADEMISCH ZIEKENHUIS LEIDEN		

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	First Named Inventor	WILTON, Stephen
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	NPL211	FRAZIER, Kendall S. et al., "Species-specific Inflammatory Responses as a Primary Component for the Development of Glomerular Lesions in Mice and Monkeys Following Chronic Administration of a Second-generation Antisense Oligonucleotide," Toxicologica Pathology, 13 pages (2013)	
	NPL212	FRIEDMANN, Theodore, "Progress Toward Human Gene Therapy," Science, Vol. 244(4910):1275-1281 (1989)	
	NPL213	GEBSKI, Bianca L. et al., "Morpholino antisense oligonucleotide induced dystrophin exon 23 skipping in mdx mouse muscle," Human Molecular Genetics, Vol. 12(15):1801-1811 (2003)	
	NPL214	Generic Method for Average Mass Determination Using LC-UV-MS in the Negative Mode, Pages 15, Exhibit Number 1145 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	NPL215	Generic UPLC Purity Method for Oligonucleotides (19- to 25-mers), Pages 18, Exhibit Number 1156 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	NPL216	GENNARO, Alfonso R., (ed.), Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing, Co., Easton PA, 2020 pages (1990)	
	NPL217	GILES, Richard V. et al., "Antisense Morpholino Oligonucleotide Analog Induces Missplicing of C-myc mRNA," Antisense & Nucleic Acid Drug Development, Vol. 9:213-220 (1999)	
	NPL218	GlaxoSmithKline Press Release, Issued in London, UK, dated June 27, 2013 (5 pages), Exhibit Number 1202 filed in Interferences 106,007 and 106,008 on February 17, 2015.	
	NPL219	GlaxoSmithKline, "GSK and Prosensa announce start of Phase III study of investigational Duchenne Muscular Dystrophy medication," press release, 6 pages, dated January 19, 2011 (Exhibit Number 2060 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL220	GlaxoSmithKline, "Prosensa regains rights to drisapersen from GSK and retains rights to all other programmes for the treatment of Duchenne muscular dystrophy (DMD), press release, 4 pages, dated January 13, 2014 (Exhibit 2040 in Interferences 106007, 106008, and 106013 on November 18, 2014).	
	NPL221	GOEMANS, Nathalie M. et al., "Systemic Administration of PRO051 in Duchenne's Muscular Dystrophy," The New England Journal of Medicine, Vol. 364:1513-1522 (2011) (Exhibit Number 2036 filed in interferences 106008, 106013, 106007 on November 18, 2014)	

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	NPL222	GORDON, Peter M. et al., "Metal ion catalysis during the exon-ligation step of nuclear pre-mRNA splicing: Extending the parallels between the spliceosome and group II introns," RNA, Vol. 6:199-205 (2000) (Exhibit Number 1055 filed in interferences 106008, 106007 on November 18, 2014)	
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	NPL228	Laboratory Notebook Entry (Exon 51 Experiments): Transfection of KM155.C25 Cells, Pages 1, Exhibit Number 1171 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	NPL229	Laboratory Notebook Entry (Exon 53 Experiments): RT-PCR Analysis of KM155.C25 Cells, Pages 2, Exhibit Number 1180 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	NPL230	Laboratory Notebook Entry (Exon 53 Experiments): RT-PCR Analysis of R1809 Cells, Pages 2, Exhibit Number 1181 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	NPL231	Laboratory Notebook Entry (Exon 53 Experiments): Transfection of KM155.C25 Cells, Pages 1, Exhibit Number 1173 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	NPL232	Laboratory Notebook Entry (Exon 53 Experiments): Transfection of R1809 Cells, Pages 1, Exhibit Number 1174 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	NPL233	Laboratory Notebook Entry: General RNA recovery, 1 Page, Exhibit Number 1176 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
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	NPL275	MOULTON, Hong M. et al., "Morpholinos and their peptide conjugates: Therapeutic promise and challenge for Duchenne muscular dystrophy," Biochimica et Biophysica Acta, Vol. 1798:2296-2303 (2010)	
	NPL276	Muntoni F, et al., "Dystrophin and mutations: one gene, several proteins, multiple phenotypes," Lancet Neurol. 2003;2:731-40.	
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	NPL279	NELSON, David L. et al., "Nucleotides and Nucleic Acids," Lehninger Principles of Biochemistry, 3rd Edition, Chapter 10, pages 325-328 and glossary page G-11, Worth Publishers, New York (2000)	
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	NPL290	Popplewell, et al., Design of Phosphorodiamidate Morpholino Oligomers (PMOs) For the Induction of Exon Skipping of the Human DMD Gene, DSGT Poster, 2008, 1 page.	
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	NPL300	Program Schedule for The Tenth Annual Meeting of the RNA Society, held at the Banff Centre for Conferences, in Banff, Alberta, Canada, from May 24-29, 2005, (University of Western Australia Exhibit 2136, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-4).	
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	NPL309	Reply to EPO Communication dated October 21, 2014 in European Application Serial No. 12198517, (University of Western Australia Exhibit 2148, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-7).	
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	NPL523	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Motion 3 Requesting an additional Interference between UWA U.S. Patent No. 8,455,636 and AZL USSN 14/248,279, 36 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 212)	
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	NPL525	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Filing Priority Statement, 2 pages, Patent Interference No. 106,008, dated November 18, 2014 (Doc 218)	
	NPL526	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,007, July 2, 2015, pages 1-16 (Doc 469).	
	NPL527	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,007, September 2, 2015, pages 1-18 (Doc 470).	

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	Examiner Name	K. Chong
	Attorney Docket Number	4140.01500B1

	NPL528	US Application No. 14/248,279, 29 pages; excerpts of prosecution history including: Amendment under 37 CFR 1.312 dated September 19, 2014; Amendment in Response to Final Office Action dated August 7, 2014; Declaration under 37 CFR 1.132 dated May 26, 2014; Declaration under 37 CFR 1.132 dated May 27, 2014; Response dated June 3, 2014 (Exhibit Number 2057 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL529	US Application No.13/550,210, 27 pages; excerpts of prosecution history including: Response and Amendment dated May 12, 2014; Response to Non-Final Office Action dated January 21, 2014; Second Preliminary Amendment dated January 3, 2013 (Exhibit Number 2055 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL530	US claim amendments for Application No. 13/550,210, 3 pages, dated May 12, 2014 (Exhibit Number 2078 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL531	US Claims for Application No. 12/976,381, 1 page, dated December 22, 2010 (Exhibit Number 2065 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL532	US Declaration of Richard K. Bestwick, for Application No. 11/570,691, 5 pages, dated June 15, 2010 (Exhibit Number 1044 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL533	US E-mail from Patent Trial and Appeal Board to Danny Huntington, 2 pages, dated October 9, 2014 (Exhibit Number 2002 filed in interferences 106008 on October 17, 2014)	
	NPL534	US Non-Final Office Action for Application No. 11/570,691, 16 pages, dated March 15, 2010 (Exhibit Number 1042 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL535	US Office Action for Application No. 13/271,080, 25 pages, dated July 30, 2012 (Exhibit Number 1048 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL536	US Office Action for Application No. 13/550,210, 12 pages, dated September 27, 2013 (Exhibit Number 2080 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL537	US Office Action for Application No. 13/902,376, 7 pages, dated January 7, 2014 (Exhibit Number 1045 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL538	US Patent Application No. 12/198,007 as-filed, 64 pages, dated August 25, 2008 (Exhibit Number 2092 filed in interferences 106008, 106013, and 106007 on November 18, 2014)	

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	NPL539	US Preliminary Amendment and application as-filed for Application No. 12/976,381,64 pages, dated December 22, 2010 (Exhibit No. 2089 filed in Interferences 106007, 106008, and 106013 on November 18, 2014)	
	NPL540	US Preliminary Amendment for Application No. 11/233,495, 10 pages, dated September 21, 2005 (Exhibit Number 2069 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL541	US Preliminary Remarks for Application No. 14/198,992, 1 page, dated March 6, 2014 (Exhibit Number 2097 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL542	US Proposed Terminal Disclaimer for Application No. 12/860,078, 2 pages, dated October 17, 2014 (Exhibit Number 2001 filed in interference 106008 on October 17, 2014)	
	NPL543	US Remarks for Application No. 14/248,279, 2 pages, dated August 27, 2014 (Exhibit Number 2110 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL544	US Response and amendments for Application No. 13/550,210, 12 pages, dated January 21, 2014 (Exhibit Number 2063 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL545	US Revised Figure 4H, US Application No. 13/271,080, 1 page (Exhibit Number 1050 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL546	US Terminal Disclaimer for Application No. 14/198,992, 1 page, dated July 15, 2014 (Exhibit Number 2096 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL547	US Terminal Disclaimer for Application No. 14/248,279, 1 page, dated August 7, 2014 (Exhibit Number 2109 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL548	US Track One Request, Application as-filed, and Application Data Sheet for Application No. 14/248,279, 68 pages, dated April 8, 2014 (Exhibit Number 2108 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL549	US Transmittal, application as-filed, and Preliminary Amendment for Application No. 11/570,691, 102 pages, dated December 15, 2006 (Exhibit Number 2103 filed in interferences 106008, 106013, 106007 on November 18, 2014)	

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	NPL550	US Transmittal, application as-filed, and Preliminary Amendment for Application No. 13/270,992, 101 pages, dated October 11, 2011 (Exhibit Number 2098 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL551	US Transmittal, application as-filed, and Preliminary Amendment for Application No. 13/271,080, 115 pages, dated October 11, 2011 (Exhibit Number 2111 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL552	US Updated Filing Receipt for Application No. 13/550,210, 3 pages, dated December 11, 2012 (Exhibit Number 2044 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL553	USPTO "2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving...Natural Products" ("the March Guidance"), 19 pages, (Exhibit Number 2118 filed in interferences 106,007 and 106,008 on February 17, 2015.	
	NPL554	USPTO Written Description Training Materials, Revised March 25, 2008, Example 12, 6 pages, (Exhibit Number 1068 filed in interferences 106008, 106007 on December 23, 2014)	
	NPL555	UWA Clean Copy of Claims and Sequence, as filed in Interference No. 106,007 on August 1, 2014 (Paper 12), 8 pages, (Exhibit Number 2126 filed in interferences 106,007 and 106,008 on February 17, 2015.	
	NPL556	UWA Clean Copy of Claims and Sequence, as filed in Interference No. 106,007 on August 7, 2014 (Paper 12), 8 pages, (Exhibit Number 2127 filed in interferences 106,007 and 106,008 on February 17, 2015.	
	NPL557	UWA Motion 1 (For Judgment Under 35 § 112(a)) from Int. No. 106,007 (PN210), 40 Pages, Exhibit Number 1005 filed in Interference 106,013 on February 17, 2015.	
	NPL558	UWA Motion 1 (For Judgment Under 35 § 112(a)) from Int. No. 106,008 (Doc 213), Pages 38, Exhibit Number 1004 filed in Interference 106,013 on February 17, 2015.	
	NPL559	UWA submission of teleconference transcript , 28 pages, dated December 12, 2014 (Exhibit Number 2114 filed in interferences 106008 and 106007 on December 12, 2014)	
	NPL560	Valorization Memorandum published by the Dutch Federation of University Medical Centers in March 2009, (University of Western Australia Exhibit 2140, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-33).	

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	NPL561	VAN DEUTEKOM et al., "Antisense-induced exon skipping restores dystrophin expression in DMD patient derived muscle cells," HUMAN MOLECULAR GENETICS Vol. 10, No. 15: 1547-1554 (2001) (Exhibit Number 1084 filed in Interferences 106008, 106007 on December 23, 2014)	
	NPL562	van Deutekom et al., "Local Dystrophin Restoration with Antisense Oligonucleotide PRO051," N. Engl. J. Med., Vol. 357, No. 26, pp. 2677-2686 (December, 2007), Exhibit Number 1213 filed in Interferences 106,007 and 106,008 on February 17, 2015.	
	NPL563	VAN DEUTEKOM, Judith C. T. et al., "Advances in Duchenne Muscular Dystrophy Gene Therapy," Nature Reviews Genetics, Vol. 4(10):774-783 (2003)	
	NPL564	Van Ommen 2002 PCT (WO 02/24906 Al), 43 pages,(Exhibit Number 1071 filed in interferences 106008, 106007 on December 23, 2014)	
	NPL565	van Putten M, et al., "The Effects of Low Levels of Dystrophin on Mouse Muscle Function and Pathology. PLoS ONE 2012;7:e31937, 13 pages	
	NPL566	Van Vliet, Laura et al., "Assessment of the Feasibility of Exon 45-55 Multiexon Skipping for Duchenne Muscular Dystrophy", BMC Medical Genetics, Vol.9(1):105 (2008)	
	NPL567	VERMA, Sandeep et al., "Modified Oligonucleotides: Synthesis and Strategy for Users," Annu. Rev. Biochem., Vol. 67:99-134 (1998) (Exhibit Number 1040 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL568	Vikase Corp. v. Am. Nat'l. Can Co., No. 93-7651, 1996 WL 377054 (N.D. Ill. July 1, 1996), 3 pages (Exhibit Number 2152 filed in interference 106013 on October 29, 2015)	
	NPL569	VOIT, Thomas et al., "Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): an exploratory, randomised, placebo-controlled phase 2 study," Lancet Neurol., Vol. 13:987-996 (2014) (Exhibit Number 2037 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL570	VOLLOCH, Vladimir et al., "Inhibition of Pre-mRNA Splicing by Antisense RNA in Vitro: Effect of RNA Containing Sequences Complementary to Exons," Biochemical and Biophysical Research Communications, Vol. 179 (3):1593-1599 (1991)	
	NPL571	Wahlestedt et al., "Potent and nontoxic antisense oligonucleotides containing locked nucleic acids," PNAS, Vol. 97, No. 10, pp. 5633-5638 (May, 2000), Exhibit Number 1201 filed in Interferences 106,007 and 106,008 on February 17, 2015.	

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	NPL572	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,008, July 2, 2015, pages 1-16 (Doc 477).	
	NPL573	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,008, September 2, 2015, pages 1-18 (Doc 478).	
	NPL574	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Related Proceedings, Patent Interference No. 106,007, 3 pages, dated August 1, 2014 (Doc 11)	
	NPL575	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Related Proceedings, Patent Interference No. 106,008, 5 pages, dated August 7, 2014 (Doc 11)	
	NPL576	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Related Proceedings, Patent Interference No. 106,013, 3 pages, dated October 14, 2014 (Doc 6)	
	NPL577	US 7,960,541 (Wilton et al.), Pages 84, Exhibit Number 1002 filed in interferences 106,007 and 106,008 on November 18, 2014.	
	NPL578	US 8,450,474 (Wilton et al.), Pages 95, Exhibit Number 1087 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL579	US 8,455,634 (Wilton et al.) Pages 96, Exhibit Number 1088 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL580	US 8,455,635 (Wilton et al.), Pages 96, Exhibit Number 1089 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL581	US 8,455,636 (Wilton et al.), Pages 92, Exhibit Number 1003 filed in interferences 106,007 and 106,008 on November 18, 2014.	
	NPL582	US 8,476,423 (Wilton et al.), Pages 95, Exhibit Number 1111 filed in interferences 106,007 and 106,008 on February 13, 2015.	

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	NPL583	US 8,501,703 (Bennett et al.), Pages 16, Exhibit Number 1090 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL584	US 8,501,704 (Mourich et al.), Pages 39, Exhibit Number 1091 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL585	US 8,524,676 (Stein et al.), Pages 28, Exhibit Number 1092 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL586	US 8,524,880 (Wilton et al.), Pages 89, Exhibit Number 1093 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL587	US 8,536,147 (Weller et al.), Pages 95, Exhibit Number 1094 filed in interferences 106,007 and 106,008 on February 17, 2015.	
	NPL588	US 8,592,386 (Mourich et al.), Pages 46, Exhibit Number 1095 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL589	US 8,618,270 (Iversen et al.), Pages 28, Exhibit Number 1096 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL590	US 8,637,483 (Wilton et al.), Pages 157, Exhibit Number 1097 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL591	US 8,697,858 (Iversen), Pages 95, Exhibit Number 1098 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL592	US 8,703,735 (Iversen et al.) Pages 73, Exhibit Number 1099 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL593	US 8,741,863 (Moulton et al.), Pages 68, Exhibit Number 1100 filed in interferences 106,007 and 106,008 on February 13, 2015.	

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	NPL594	US 8,759,307 (Stein et al.), Pages 35, Exhibit Number 1101 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL595	US 8,779,128 (Hanson et al.), Pages 104, Exhibit Number 1102 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL596	US 8,785,407 (Stein et al.), Pages 35, Exhibit Number 1103 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL597	US 8,785,410 (Iversen et al.), Pages 20, Exhibit Number 1104 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL598	US 8,835,402 (Kole et al.), Pages 27, Exhibit Number 1105 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL599	US 8,865,883 (Sazani et al.), Pages 199, Exhibit Number 1106 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL600	US 8,871,918 (Sazani et al.), Pages 195, Exhibit Number 1107 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL601	US 8,877,725 (Iversen et al.), Pages 34, Exhibit Number 1108 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL602	US 8,895,722 (Iversen et al.), Pages 29, Exhibit Number 1109 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL603	US 8,906,872 (Iversen et al.), Pages 69, Exhibit Number 1110 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL604	US Abandonment for Application No. 13/902,376, 1 page, dated June 12, 2014 (Exhibit Number 1047 filed in Interferences 106008, 106007 on November 18, 2014)	

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	NPL605	US Amendment After Non-Final Action for Application No. 11/233,495, 31 pages, dated June 24, 2010 (Exhibit Number 2073 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL606	US Amendment for Application No. 11/233,495, 15 pages, dated April 1, 2009 (Exhibit Number 2071 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL607	US Amendment for Application No. 11/233,495, 19 pages, dated September 16, 2009 (Exhibit Number 2072 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL608	US Amendment for Application No. 11/233,495, 9 pages, dated October 31, 2007 (Exhibit Number 2070 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL609	US Amendment for Application No. 11/570,691, 9 pages, dated June 15, 2010 (Exhibit Number 1043 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL610	US Amendment for Application No. 13/271,080, 30 pages, dated January 30, 2013 (Exhibit Number 1049 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL611	US Amendment for Application No. 13/902,376, 36 pages, dated March 21, 2014 (Exhibit Number 1046 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL612	US Amendment in Response to Advisory Action for Application No. 11/233,495, 23 pages, dated March 14, 2011 (Exhibit Number 2074 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL613	US Amendments to the Claims for Application No. 11/233,495, 4 pages, dated May 8, 2014 (Exhibit Number 2077 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL614	US Amendments to the Claims for Application No. 14/198,992, 3 pages, dated July 16, 2014 (Exhibit Number 2079 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL615	US Applicant-Initiated Interview Summary and Notice of Allowance for Application No. 13/550,210, 9 pages dated May 19, 2014 (Exhibit Number 2076 filed in interferences 106008, 106013, 106007 on November 18, 2014)	

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	NPL616	US application as-filed and Preliminary Amendment for Application No. 13/550,210, 59 pages dated July 16, 2012 (Exhibit Number 2087 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL617	US Application as-filed for application No. 14/198,992, 52 pages, dated March 6, 2014 (Exhibit Number 2086 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL618	US Application as-filed, Application Data Sheet, and Preliminary Amendment for Application No. 12/837,359, 101 pages, dated July 15, 2010 (Exhibit Number 2100 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL619	US Application for Letters Patent for Application No. 11/233,495 as-filed and preliminary amendment, 77 pages, dated September 21, 2005 (Exhibit Number 2095 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL620	US Application No. 11/233,495, 74 pages; excerpts of prosecution history including: US Supplemental Amendment and Response dated May 8, 2014; Second Supplemental Response dated July 25, 2013; Supplemental Amendment dated June 26, 2013; Amendment after Non-final Action dated November 1, 2010; Amendment under 35 USC 1.114 dated September 16, 2009 (Exhibit Number 2054 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL621	US Application No. 14/198,992, 17 pages; excerpts of prosecution history including: Supplemental Amendment dated July 16, 2014; Response to Non-Final Office Action dated July 14, 2014 (Exhibit Number 2056 filed in interferences 106008, 106013, 106007 on November 18, 2014)	

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	NPL622	WILTON, Stephen D. et al., "Antisense oligonucleotides in the treatment of Duchenne muscular dystrophy: where are we now?" Neuromuscular Disorders, Vol. 15:399-402 (2005)	
	NPL623	WILTON, Stephen D. et al., "Specific removal of the nonsense mutation from the mdx dystrophin mRNA using antisense oligonucleotides," Neuromuscular Disorders, Vol. 9:330-338 (1999)	
	NPL624	WO 2002/24906 A1 of AZL, (University of Western Australia Exhibit 2134, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-43.)	
	NPL625	WO 2004/083432 (the published AZL PCT Application, "Van Ommen"), Pages 71, Exhibit Number 1003 filed in Interference 106,013 on February 17, 2015.	
	NPL626	WO 2013/112053 A1, (University of Western Australia Exhibit 2130, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-177).	
	NPL627	WOLFF, Jon A. et al., "Direct Gene Transfer into Mouse Muscle in Vivo," Science, Vol. 247:1465-1468 (1990)	
	NPL628	WONG, Marisa L. et al., "Real-time PCR for mRNA quantitation," BioTechniques, Vol. 39:75-85 (2005) (Exhibit Number 1066 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL629	Wood, "Toward an Oligonucleotide Therapy for Duchenne Muscular Dystrophy: A Complex Development Challenge," Science Translational Medicine, Vol. 2, No. 25, pp. 1-6 (March, 2010), Exhibit Number 1116 filed in interferences 106,007 and 106,008 on February 17, 2015,Doc 335.	
	NPL630	Written Opinion for Application No. PCT/AU2010/001520, 6 pages, dated January 21, 2011	
	NPL631	WU, B. et al., "Dose-dependent restoration of dystrophin expression in cardiac muscle of dystrophic mice by systemically delivered morpholino," Gene Therapy, Vol. 17:132-140 (2010)	
	NPL632	WU, Bo et al., "Effective rescue of dystrophin improves cardiac function in dystrophin-deficient mice by a modified morpholino oligomer," PNAS, Vol. 105(39):14814-14819 (2008)	

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	Art Unit	1635
	Examiner Name	K. Chong
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
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	NPL709	Office Action mailed July 12, 2018, in United States Patent Application No. 15/645,842, Wilton et al., filed July 10, 2017, 19 pages	
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Filing Date:	24-Aug-2018
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Filer:	Neil P. Shull/Debbie Colonna
Attorney Docket Number:	4140.01500B1

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Application Number:	16112453
International Application Number:	
Confirmation Number:	3144
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	153767
Filer:	Neil P. Shull/Debbie Colonna
Filer Authorized By:	Neil P. Shull
Attorney Docket Number:	4140.01500B1
Receipt Date:	17-JAN-2019
Filing Date:	24-AUG-2018
Time Stamp:	16:35:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$120
RAM confirmation Number	011819INTEFSW16362000
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		4140_01500B1_Amendment_Reply.pdf	117936 9f30ba491cff0523553b70685f0997f93e061219	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	2
	Applicant Arguments/Remarks Made in an Amendment	3	6

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
2	Transmittal Letter	4140_01500B1_IDS_Pleading.pdf	118365 4b1d4923f460f6ca56448cc89eb2d859ec9851c8	no	7

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
3	Information Disclosure Statement (IDS) Form (SB08)	4140_01500B1_IDS_Form_08a_08b.pdf	3244431 c817d588c489d2fc2f59b85d1dff3fee2fa24efa	no	111

Warnings:

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This is not an USPTO supplied IDS fillable form

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
4	Information Disclosure Statement (IDS) Form (SB08)	4140_01500B1_IDS_Form_08b.pdf	117461 6683dcb25ef58690e19db7aafc96de364616b1ec	no	1

Warnings:

Information:

This is not an USPTO supplied IDS fillable form

5	Non Patent Literature	NPL709_OA_15645842_07122018.PDF	1070489 b2652239d9aa211887f7b618bb322b5b90c06e7c	no	20
Warnings:					
Information:					
6	Non Patent Literature	NPL710_NFOA_15655646_07312018.PDF	760181 0cc4bf8872ce3927586d536cb5982d03706abc57	no	16
Warnings:					
Information:					
7	Non Patent Literature	NPL711_OA_15673019_09072018.PDF	351983 6f183500377fb479091b657f104936290d71ff0a	no	9
Warnings:					
Information:					
8	Non Patent Literature	NPL712_Koenig_1989.PDF	633941 4fcf2caf4917ccb67ae3d1a3c48638c0de830165	no	3
Warnings:					
Information:					
9	Non Patent Literature	NPL713_Takeshima.PDF	727124 4c6c7c321f8ff4b8d39690979f2fd70dfb80361a	no	7
Warnings:					
Information:					
10	Non Patent Literature	NPL714_OA_1018201.PDF	213648 4e89d10f8902cb12b8d545b133d8171e835170a0	no	6
Warnings:					
Information:					
11	Fee Worksheet (SB06)	fee-info.pdf	30593 57d9e312ba6917939d270585f65153d00875e869	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	7386152		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

153767 7590 02/12/2019
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/12/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/112,453	08/24/2018	Stephen Donald WILTON	4140.01500B1	3144

TITLE OF INVENTION: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	05/13/2019

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

153767 7590 02/12/2019
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/112,453	08/24/2018	Stephen Donald WILTON	4140.01500B1	3144

TITLE OF INVENTION: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	05/13/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHONG, KIMBERLY	1635	514-04400A

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 ______
2 ______
3 ______

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies ______

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. ______

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature ______ Date ______

Typed or printed name ______ Registration No. ______

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/112,453	08/24/2018	Stephen Donald WILTON	4140.01500B1	3144

153767 7590 02/12/2019
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/12/2019

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	**Application No.** 16/112,453	**Applicant(s)** WILTON et al.	
	Examiner KIMBERLY CHONG	**Art Unit** 1635	**AIA Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1.☑ This communication is responsive to 01/17/2019.
  ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ______.

2.☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ______; the restriction requirement and election have been incorporated into this action.

3.☑ The allowed claim(s) is/are 1-2 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4.☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ______ .
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: ______ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5.☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
  ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ______ .

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6.☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1.☐ Notice of References Cited (PTO-892)
2.☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 01/17/2019.
3.☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material ______.
4.☐ Interview Summary (PTO-413), Paper No./Mail Date. ______.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other ______.

/KIMBERLY CHONG/
Primary Examiner, Art Unit 1635

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: the amendments filed 01/17/2019 have overcome the rejections of record. Claims 1 and 2 are in condition for allowance.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **KIMBERLY CHONG at (571)272-3111**. The examiner can normally be reached Monday thru Friday between M-F 8:00am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1674 Ram Shukla at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

(EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1635

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/112,453	WILTON et al.
	Examiner	Art Unit
	KIMBERLY CHONG	1635

CPC

Symbol					Type	Version
C12N	/	15	/	113	F	2013-01-01
C12N	/	2320	/	30	A	2013-01-01
C12N	/	2310	/	3341	A	2013-01-01
C12N	/	2310	/	321	A	2013-01-01
C12N	/	2310	/	315	A	2013-01-01
C12N	/	2310	/	33	A	2013-01-01
C12N	/	2310	/	3233	A	2013-01-01
C12N	/	2310	/	11	A	2013-01-01
C12N	/	2320	/	33	A	2013-01-01
C12N	/	2310	/	3519	A	2013-01-01

CPC Combination Sets

Symbol					Type	Set	Ranking	Version
	/		/					

NONE (Assistant Examiner) (Date)	Total Claims Allowed: 2	
/KIMBERLY CHONG/ 04 February 2019 Primary Examiner, Art Unit 1635 (Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No.: 20190204

Issue Classification	Application/Control No. 16/112,453	Applicant(s)/Patent Under Reexamination WILTON et al.
	Examiner KIMBERLY CHONG	Art Unit 1635

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C07H	/	21	/	04

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
536	24.5

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE (Assistant Examiner)	(Date)	Total Claims Allowed: 2	
/KIMBERLY CHONG/ Primary Examiner, Art Unit 1635 (Primary Examiner)	04 February 2019 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification	Application/Control No. 16/112,453	Applicant(s)/Patent Under Reexamination WILTON et al.
	Examiner KIMBERLY CHONG	Art Unit 1635

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE (Assistant Examiner) (Date)	Total Claims Allowed: 2	
/KIMBERLY CHONG/ 04 February 2019 Primary Examiner, Art Unit 1635 (Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office Part of Paper No.: 20190204

SRPT-VYDS-0006476

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/112,453	WILTON et al.
	Examiner	**Art Unit**
	KIMBERLY CHONG	1635

CPC - Searched*		
Symbol	**Date**	**Examiner**
C07H 21/04	12/19/2018	KC

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

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Search Notes		
Search Notes	**Date**	**Examiner**
C07H 21/04	12/19/2018	KC
SEQ ID No. 195	12/18/2018	KC
PALM inventor name search	12/18/2018	KC
updated	02/04/2019	KC

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
536	24.5	02/04/2019	KC

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	16/112,453
	Filing Date	August 24, 2018
	First Named Inventor	WILTON, Stephen
	Art Unit	1635
	Examiner Name	K. Chong
	Attorney Docket Number	4140.01500B1

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	NPL1	Extended European Search Report, EP 17159328.8, dated September 5, 2017, 10 pages.

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Examiner Initial*	Cite No	Patent Number	Kind Code1	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	US1	9506058		2016-11-29	Kaye	
	US2	9605262		2017-03-28	Wilton et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code1	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	US3	20130190390	A1	2013-07-25	SAZANI et al.	
	US4	20170009233	A1	2017-01-12	WILTON et al.	

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	FP1	2013/142087	WO	A1	2013-09-26	Sarepta Therapeutics, Inc		

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	FP2	2014/172669	WO	A1	2014-10-23	Research Institute at Nationwide Children's Hosp.		
	FP3	2017/059131	WO	A1	2017-04-06	Sarepta Therapeutics, Inc		

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	NPL2	GenBank AF213437.1 Dated January 17, 2002	
	NPL3	International Search Report and Written Opinion, PCT/US2016/054534, dated January 17, 2017, 13 pages.	
	NPL4	KOLE et al., "Exon skipping therapy for Duchenne muscular dystrophy," Advanced Drug Delivery Reviews, vol. 87:104-107 (2015).	
	NPL5	WHO Drug Information, International Nonproprietary Names for Pharmaceutical Substances (INN), Proposed INN: List 115, "CASIMERSEN," vol. 30(2): 3 pages (2016)	
	NPL6	WHO Drug Information, International Nonproprietary Names for Pharmaceutical Substances (INN), Proposed INN: List 115, "Golodirsen," vol. 30(2): 3 pages (2016)	

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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Examiner Initial*	Cite No	Patent Number	Kind Code1	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	US5	8436163		2013-05-07	Iversen et al.	
	US6	9416361		2016-08-16	Iversen et al.	

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	US7	20040266720	A1	2004-12-30	Iversen et al.	
	US8	20120053228	A1	2012-03-01	Iversen et al.	
	US9	20140045916	A1	2014-02-13	Iversen et al.	
	US10	20150232839	A1	2015-08-20	Iversen et al.	

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	US11	20160298111	A1	2016-10-13	Bestwick et al.	

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	US12	9453225		2016-09-27	Sazani et al.	
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	US15	9447415		2016-09-20	Wilton et al.	
	US16	9441229		2016-09-13	Wilton et al.	
	US17	9434948		2016-09-06	Sazani et al.	
	US18	9422555		2016-08-23	Wilton et al.	

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	US19	20160177301	A1	2016-06-23	Wilton et al.	

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	NPL7	Errata to the Sarepta Briefing Information for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Eteplirsen Errata Document, NDA 206488, 5 pages.	
	NPL8	Extended European Search Report, EP 15190341.6, dated April 28, 2016, 9 pages.	
	NPL9	FDA Briefing Information for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Eteplirsen, NDA 206488, 115 pages	
	NPL10	FDA News Release, "FDA grants accelerated approval to first drug for Duchenne muscular dystrophy," September 19, 2016, 3 pages.	

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	NPL11	Jett Foundation Presentation by McSherry, C. "Patient and Caregiver-Reported Outcomes of Patients in Clinical Trials of Eteplirsen for Treatment of Duchenne" at Peripheral and Central Nervous System Drugs Advisory Committee, April 25, 2016, 17 pages.	
	NPL12	Letter from the FDA to Sarepta Therapeutics, Inc., Re: ACCELERATED APPROVAL for the use of Exondys 51 (eteplirsen), FDA Reference ID: 3987286, dated September 19, 2016, 11 pages.	
	NPL13	Letter to the U.S. Food and Drug Administration, (Dr. Billy Dunn, M.D. Director Division of Neurology Products, Office of Drug Evaluation 1, Center for Drug Evaluation and Research), for The Peripheral and Central Nervous System Advisory Committee Meeting (AdComm) supporting approval of eteplirsen, dated February 24, 2016, 4 pages.	
	NPL14	Letter to the U.S. Food and Drug Administration, (Dr. Janet Woodcock, M.D. Director, CDER), from The Congress of The United States regarding Duchenne muscular dystrophy, dated February 17, 2016, 7 pages.	
	NPL15	Prescribing Information for EXONDYS 51 (eteplirsen) Injection, dated 09/2016, 10 pages	
	NPL16	Sarepta Briefing Information for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Eteplirsen Briefing Document, NDA 206488, 186 pages.	
	NPL17	Sarepta Presentation at Peripheral and Central Nervous System Drugs Advisory Committee, April 25, 2016, 133 pages	
	NPL18	Sarepta Press Release, Sarepta Issues Statement on Advisory Committee Outcome for Use of Eteplirsen in the Treatment of Duchenne Muscular Dystrophy, April 25, 2016, 2 pages	
	NPL19	Sarepta Therapeutics, Inc. News Release, "Sarepta Therapeutics Announces FDA Accelerated Approval of EXONDYS 51™ (eteplirsen) injection, an Exon Skipping Therapy to Treat Duchenne Muscular Dystrophy (DMD) Patients Amenable to Skipping Exon 51," September 19, 2016, 2 pages.	
	NPL20	U.S. Food and Drug Administration Presentation at Peripheral and Central Nervous System Drugs Advisory Committee, April 25, 2016, 178 pages.	
	NPL21	University of Western Australia v. Academisch Ziekenhuis Leiden, Decision - Motions - 37 C.F.R. § 41.125(a), filed in Patent Interference No. 106008, September 20, 2016, pages 1-20 (Doc 480)	

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	NPL22	University of Western Australia v. Academisch Ziekenhuis Leiden, Decision - Motions - 37 CFR § 41.125(a) (Substitute), filed in Patent Interference No. 106007, May 12, 2016, pages 1-53 (Doc 476)	
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	NPL27	University of Western Australia v. Academisch Ziekenhuis Leiden, Decision - Motions - 37 CFR § 41.125(a), filed in Patent Interference No. 106007, April 29, 2016, pages 1-53, (Doc 472)	

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	FP7	2002-340857	JP	A	2002-11-27	MATSUSHITA ELECTRIC IND CO LTD		
	FP8	2002-529499	JP	A	2002-09-10	ELI LILLY AND COMPANY		
	FP9	2004-509622	JP	A	2004-04-02	ACADEMISCH ZIEKENHUIS LEIDEN		
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	FP11	2011-101655	JP	A	2011-05-26	ACADEMISCH ZIEKENHUIS LEIDEN		
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	FP13	2014-054250	JP	A	2014-03-27	NIPPON SHINYAKU CO LTD.		
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	FP22	00/78341	WO	A1	2000-12-28	Murdoch Childrens Research Institute		
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	FP24	01/72765	WO	A1	2001-10-04	ISIS Pharmaceuticals, Inc.		
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	FP29	02/29406	WO	A1	2002-04-11	Murto, James		
	FP30	03/053341	WO	A2	2003-07-03	Isis Pharmaceuticals, Inc.		
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	FP35	2006/000057	WO	A1	2006-01-05	University of Western Australia		☐
	FP36	2006/021724	WO	A2	2006-03-02	Genethon et al.		☒
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	FP38	2007/058894	WO	A2	2007-05-24	The University of North Carolina at Chapel Hill et		☐
	FP39	2007/133812	WO	A2	2007-11-22	Philadelphia Health & Education Corporation, D/B/A		☐

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	FP40	2007/135105	WO	A1	2007-11-29	Academisch Ziekenhuis Leiden		☐
	FP41	2008/036127	WO	A2	2008-03-27	Avi Biopharma, Inc.		☐
	FP42	2009/054725	WO	A2	2009-04-30	Academisch Ziekenhuis Leiden et al.		☐
	FP43	2009/101399	WO	A1	2009-08-20	Isis Innovation Limited		☐
	FP44	2009/139630	WO	A2	2009-11-19	Prosensa Technologies B.V. et al.		☐
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	Examiner Name	K. Chong
	Attorney Docket Number	4140.01500B1

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	Art Unit	1635
	Examiner Name	K. Chong
	Attorney Docket Number	4140.01500B1

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	NPL522	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Motion 3 (For judgment that Claims 11-12, 14-15, and 17-29 of Application No. 13/550,210 are barred under 35 U.S.C. section 135(b)), 25 Pages, Patent Interference No. 106,008, dated November 18, 2014 (Doc 215)	
	NPL523	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Motion 3 Requesting an additional Interference between UWA U.S. Patent No. 8,455,636 and AZL USSN 14/248,279, 36 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 212)	
	NPL524	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Filing Priority Statement, 2 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 215)	
	NPL525	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Filing Priority Statement, 2 pages, Patent Interference No. 106,008, dated November 18, 2014 (Doc 218)	
	NPL526	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,007, July 2, 2015, pages 1-16 (Doc 469).	
	NPL527	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,007, September 2, 2015, pages 1-18 (Doc 470).	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/112,453
	Filing Date	August 24, 2018
	First Named Inventor	WILTON, Stephen
	Art Unit	1635
	Examiner Name	K. Chong
	Attorney Docket Number	4140.01500B1

	NPL528	US Application No. 14/248,279, 29 pages; excerpts of prosecution history including: Amendment under 37 CFR 1.312 dated September 19, 2014; Amendment in Response to Final Office Action dated August 7, 2014; Declaration under 37 CFR 1.132 dated May 26, 2014; Declaration under 37 CFR 1.132 dated May 27, 2014; Response dated June 3, 2014 (Exhibit Number 2057 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL529	US Application No.13/550,210, 27 pages; excerpts of prosecution history including: Response and Amendment dated May 12, 2014; Response to Non-Final Office Action dated January 21, 2014; Second Preliminary Amendment dated January 3, 2013 (Exhibit Number 2055 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL530	US claim amendments for Application No. 13/550,210, 3 pages, dated May 12, 2014 (Exhibit Number 2078 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL531	US Claims for Application No. 12/976,381, 1 page, dated December 22, 2010 (Exhibit Number 2065 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL532	US Declaration of Richard K. Bestwick, for Application No. 11/570,691, 5 pages, dated June 15, 2010 (Exhibit Number 1044 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL533	US E-mail from Patent Trial and Appeal Board to Danny Huntington, 2 pages, dated October 9, 2014 (Exhibit Number 2002 filed in interferences 106008 on October 17, 2014)	
	NPL534	US Non-Final Office Action for Application No. 11/570,691, 16 pages, dated March 15, 2010 (Exhibit Number 1042 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL535	US Office Action for Application No. 13/271,080, 25 pages, dated July 30, 2012 (Exhibit Number 1048 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL536	US Office Action for Application No. 13/550,210, 12 pages, dated September 27, 2013 (Exhibit Number 2080 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL537	US Office Action for Application No. 13/902,376, 7 pages, dated January 7, 2014 (Exhibit Number 1045 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL538	US Patent Application No. 12/198,007 as-filed, 64 pages, dated August 25, 2008 (Exhibit Number 2092 filed in interferences 106008, 106013, and 106007 on November 18, 2014)	

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	Examiner Name	K. Chong
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	NPL539	US Preliminary Amendment and application as-filed for Application No. 12/976,381,64 pages, dated December 22, 2010 (Exhibit No. 2089 filed in Interferences 106007, 106008, and 106013 on November 18, 2014)	
	NPL540	US Preliminary Amendment for Application No. 11/233,495, 10 pages, dated September 21, 2005 (Exhibit Number 2069 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL541	US Preliminary Remarks for Application No. 14/198,992, 1 page, dated March 6, 2014 (Exhibit Number 2097 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL542	US Proposed Terminal Disclaimer for Application No. 12/860,078, 2 pages, dated October 17, 2014 (Exhibit Number 2001 filed in interference 106008 on October 17, 2014)	
	NPL543	US Remarks for Application No. 14/248,279, 2 pages, dated August 27, 2014 (Exhibit Number 2110 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL544	US Response and amendments for Application No. 13/550,210, 12 pages, dated January 21, 2014 (Exhibit Number 2063 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL545	US Revised Figure 4H, US Application No. 13/271,080, 1 page (Exhibit Number 1050 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL546	US Terminal Disclaimer for Application No. 14/198,992, 1 page, dated July 15, 2014 (Exhibit Number 2096 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL547	US Terminal Disclaimer for Application No. 14/248,279, 1 page, dated August 7, 2014 (Exhibit Number 2109 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL548	US Track One Request, Application as-filed, and Application Data Sheet for Application No. 14/248,279, 68 pages, dated April 8, 2014 (Exhibit Number 2108 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL549	US Transmittal, application as-filed, and Preliminary Amendment for Application No. 11/570,691, 102 pages, dated December 15, 2006 (Exhibit Number 2103 filed in interferences 106008, 106013, 106007 on November 18, 2014)	

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	Examiner Name	K. Chong
	Attorney Docket Number	4140.01500B1

	NPL550	US Transmittal, application as-filed, and Preliminary Amendment for Application No. 13/270,992, 101 pages, dated October 11, 2011 (Exhibit Number 2098 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL551	US Transmittal, application as-filed, and Preliminary Amendment for Application No. 13/271,080, 115 pages, dated October 11, 2011 (Exhibit Number 2111 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL552	US Updated Filing Receipt for Application No. 13/550,210, 3 pages, dated December 11, 2012 (Exhibit Number 2044 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL553	USPTO "2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving...Natural Products" ("the March Guidance"), 19 pages, (Exhibit Number 2118 filed in interferences 106,007 and 106,008 on February 17, 2015.	
	NPL554	USPTO Written Description Training Materials, Revised March 25, 2008, Example 12, 6 pages, (Exhibit Number 1068 filed in interferences 106008, 106007 on December 23, 2014)	
	NPL555	UWA Clean Copy of Claims and Sequence, as filed in Interference No. 106,007 on August 1, 2014 (Paper 12), 8 pages, (Exhibit Number 2126 filed in interferences 106,007 and 106,008 on February 17, 2015.	
	NPL556	UWA Clean Copy of Claims and Sequence, as filed in Interference No. 106,007 on August 7, 2014 (Paper 12), 8 pages, (Exhibit Number 2127 filed in interferences 106,007 and 106,008 on February 17, 2015.	
	NPL557	UWA Motion 1 (For Judgment Under 35 § 112(a)) from Int. No. 106,007 (PN210), 40 Pages, Exhibit Number 1005 filed in Interference 106,013 on February 17, 2015.	
	NPL558	UWA Motion 1 (For Judgment Under 35 § 112(a)) from Int. No. 106,008 (Doc 213), Pages 38, Exhibit Number 1004 filed in Interference 106,013 on February 17, 2015.	
	NPL559	UWA submission of teleconference transcript , 28 pages, dated December 12, 2014 (Exhibit Number 2114 filed in interferences 106008 and 106007 on December 12, 2014)	
	NPL560	Valorization Memorandum published by the Dutch Federation of University Medical Centers in March 2009, (University of Western Australia Exhibit 2140, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-33).	

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	NPL561	VAN DEUTEKOM et al., "Antisense-induced exon skipping restores dystrophin expression in DMD patient derived muscle cells," HUMAN MOLECULAR GENETICS Vol. 10, No. 15: 1547-1554 (2001) (Exhibit Number 1084 filed in interferences 106008, 106007 on December 23, 2014)	
	NPL562	van Deutekom et al., "Local Dystrophin Restoration with Antisense Oligonucleotide PRO051," N. Engl. J. Med., Vol. 357, No. 26, pp. 2677-2686 (December, 2007), Exhibit Number 1213 filed in Interferences 106,007 and 106,008 on February 17, 2015.	
	NPL563	VAN DEUTEKOM, Judith C. T. et al., "Advances in Duchenne Muscular Dystrophy Gene Therapy," Nature Reviews Genetics, Vol. 4(10):774-783 (2003)	
	NPL564	Van Ommen 2002 PCT (WO 02/24906 Al), 43 pages,(Exhibit Number 1071 filed in interferences 106008, 106007 on December 23, 2014)	
	NPL565	van Putten M, et al., "The Effects of Low Levels of Dystrophin on Mouse Muscle Function and Pathology. PLoS ONE 2012;7:e31937, 13 pages	
	NPL566	Van Vliet, Laura et al., "Assessment of the Feasibility of Exon 45-55 Multiexon Skipping for Duchenne Muscular Dystrophy", BMC Medical Genetics, Vol.9(1):105 (2008)	
	NPL567	VERMA, Sandeep et al., "Modified Oligonucleotides: Synthesis and Strategy for Users," Annu. Rev. Biochem., Vol. 67:99-134 (1998) (Exhibit Number 1040 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL568	Vikase Corp. v. Am. Nat'l. Can Co., No. 93-7651, 1996 WL 377054 (N.D. Ill. July 1, 1996), 3 pages (Exhibit Number 2152 filed in interference 106013 on October 29, 2015)	
	NPL569	VOIT, Thomas et al., "Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): an exploratory, randomised, placebo-controlled phase 2 study," Lancet Neurol., Vol. 13:987-996 (2014) (Exhibit Number 2037 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL570	VOLLOCH, Vladimir et al., "Inhibition of Pre-mRNA Splicing by Antisense RNA in Vitro: Effect of RNA Containing Sequences Complementary to Exons," Biochemical and Biophysical Research Communications, Vol. 179 (3):1593-1599 (1991)	
	NPL571	Wahlestedt et al., "Potent and nontoxic antisense oligonucleotides containing locked nucleic acids," PNAS, Vol. 97, No. 10, pp. 5633-5638 (May, 2000), Exhibit Number 1201 filed in Interferences 106,007 and 106,008 on February 17, 2015.	

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	Attorney Docket Number	4140.01500B1

	NPL572	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,008, July 2, 2015, pages 1-16 (Doc 477).	
	NPL573	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,008, September 2, 2015, pages 1-18 (Doc 478).	
	NPL574	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Related Proceedings, Patent Interference No. 106,007, 3 pages, dated August 1, 2014 (Doc 11)	
	NPL575	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Related Proceedings, Patent Interference No. 106,008, 5 pages, dated August 7, 2014 (Doc 11)	
	NPL576	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Related Proceedings, Patent Interference No. 106,013, 3 pages, dated October 14, 2014 (Doc 6)	
	NPL577	US 7,960,541 (Wilton et al.), Pages 84, Exhibit Number 1002 filed in interferences 106,007 and 106,008 on November 18, 2014.	
	NPL578	US 8,450,474 (Wilton et al.), Pages 95, Exhibit Number 1087 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL579	US 8,455,634 (Wilton et al.) Pages 96, Exhibit Number 1088 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL580	US 8,455,635 (Wilton et al.), Pages 96, Exhibit Number 1089 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL581	US 8,455,636 (Wilton et al.), Pages 92, Exhibit Number 1003 filed in interferences 106,007 and 106,008 on November 18, 2014.	
	NPL582	US 8,476,423 (Wilton et al.), Pages 95, Exhibit Number 1111 filed in interferences 106,007 and 106,008 on February 13, 2015.	

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	NPL583	US 8,501,703 (Bennett et al.), Pages 16, Exhibit Number 1090 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL584	US 8,501,704 (Mourich et al.), Pages 39, Exhibit Number 1091 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL585	US 8,524,676 (Stein et al.), Pages 28, Exhibit Number 1092 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL586	US 8,524,880 (Wilton et al.), Pages 89, Exhibit Number 1093 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL587	US 8,536,147 (Weller et al.), Pages 95, Exhibit Number 1094 filed in interferences 106,007 and 106,008 on February 17, 2015.	
	NPL588	US 8,592,386 (Mourich et al.), Pages 46, Exhibit Number 1095 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL589	US 8,618,270 (Iversen et al.), Pages 28, Exhibit Number 1096 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL590	US 8,637,483 (Wilton et al.), Pages 157, Exhibit Number 1097 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL591	US 8,697,858 (Iversen), Pages 95, Exhibit Number 1098 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL592	US 8,703,735 (Iversen et al.) Pages 73, Exhibit Number 1099 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL593	US 8,741,863 (Moulton et al.), Pages 68, Exhibit Number 1100 filed in interferences 106,007 and 106,008 on February 13, 2015.	

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	Examiner Name: K. Chong
	Attorney Docket Number: 4140.01500B1

	NPL594	US 8,759,307 (Stein et al.), Pages 35, Exhibit Number 1101 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL595	US 8,779,128 (Hanson et al.), Pages 104, Exhibit Number 1102 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL596	US 8,785,407 (Stein et al.), Pages 35, Exhibit Number 1103 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL597	US 8,785,410 (Iversen et al.), Pages 20, Exhibit Number 1104 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL598	US 8,835,402 (Kole et al.), Pages 27, Exhibit Number 1105 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL599	US 8,865,883 (Sazani et al.), Pages 199, Exhibit Number 1106 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL600	US 8,871,918 (Sazani et al.), Pages 195, Exhibit Number 1107 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL601	US 8,877,725 (Iversen et al.), Pages 34, Exhibit Number 1108 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL602	US 8,895,722 (Iversen et al.), Pages 29, Exhibit Number 1109 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL603	US 8,906,872 (Iversen et al.), Pages 69, Exhibit Number 1110 filed in interferences 106,007 and 106,008 on February 13, 2015.	
	NPL604	US Abandonment for Application No. 13/902,376, 1 page, dated June 12, 2014 (Exhibit Number 1047 filed in interferences 106008, 106007 on November 18, 2014)	

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	NPL605	US Amendment After Non-Final Action for Application No. 11/233,495, 31 pages, dated June 24, 2010 (Exhibit Number 2073 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL606	US Amendment for Application No. 11/233,495, 15 pages, dated April 1, 2009 (Exhibit Number 2071 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL607	US Amendment for Application No. 11/233,495, 19 pages, dated September 16, 2009 (Exhibit Number 2072 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL608	US Amendment for Application No. 11/233,495, 9 pages, dated October 31, 2007 (Exhibit Number 2070 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL609	US Amendment for Application No. 11/570,691, 9 pages, dated June 15, 2010 (Exhibit Number 1043 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL610	US Amendment for Application No. 13/271,080, 30 pages, dated January 30, 2013 (Exhibit Number 1049 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL611	US Amendment for Application No. 13/902,376, 36 pages, dated March 21, 2014 (Exhibit Number 1046 filed in interferences 106008, 106007 on November 18, 2014)	
	NPL612	US Amendment in Response to Advisory Action for Application No. 11/233,495, 23 pages, dated March 14, 2011 (Exhibit Number 2074 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL613	US Amendments to the Claims for Application No. 11/233,495, 4 pages, dated May 8, 2014 (Exhibit Number 2077 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL614	US Amendments to the Claims for Application No. 14/198,992, 3 pages, dated July 16, 2014 (Exhibit Number 2079 filed in interferences 106008, 106013, 106007 on November 18, 2014)	
	NPL615	US Applicant-Initiated Interview Summary and Notice of Allowance for Application No. 13/550,210, 9 pages dated May 19, 2014 (Exhibit Number 2076 filed in interferences 106008, 106013, 106007 on November 18, 2014)	

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	NPL616	US application as-filed and Preliminary Amendment for Application No. 13/550,210, 59 pages dated July 16, 2012 (Exhibit Number 2087 filed in interferences 106008, 106013, 106007 on November 18, 2014)
	NPL617	US Application as-filed for application No. 14/198,992, 52 pages, dated March 6, 2014 (Exhibit Number 2086 filed in interferences 106008, 106013, 106007 on November 18, 2014)
	NPL618	US Application as-filed, Application Data Sheet, and Preliminary Amendment for Application No. 12/837,359, 101 pages, dated July 15, 2010 (Exhibit Number 2100 filed in interferences 106008, 106013, 106007 on November 18, 2014)
	NPL619	US Application for Letters Patent for Application No. 11/233,495 as-filed and preliminary amendment, 77 pages, dated September 21, 2005 (Exhibit Number 2095 filed in interferences 106008, 106013, 106007 on November 18, 2014)
	NPL620	US Application No. 11/233,495, 74 pages; excerpts of prosecution history including: US Supplemental Amendment and Response dated May 8, 2014; Second Supplemental Response dated July 25, 2013; Supplemental Amendment dated June 26, 2013; Amendment after Non-final Action dated November 1, 2010; Amendment under 35 USC 1.114 dated September 16, 2009 (Exhibit Number 2054 filed in interferences 106008, 106013, 106007 on November 18, 2014)
	NPL621	US Application No. 14/198,992, 17 pages; excerpts of prosecution history including: Supplemental Amendment dated July 16, 2014; Response to Non-Final Office Action dated July 14, 2014 (Exhibit Number 2056 filed in interferences 106008, 106013, 106007 on November 18, 2014)

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	NPL622	WILTON, Stephen D. et al., "Antisense oligonucleotides in the treatment of Duchenne muscular dystrophy: where are we now?" Neuromuscular Disorders, Vol. 15:399-402 (2005)	
	NPL623	WILTON, Stephen D. et al., "Specific removal of the nonsense mutation from the mdx dystrophin mRNA using antisense oligonucleotides," Neuromuscular Disorders, Vol. 9:330-338 (1999)	
	NPL624	WO 2002/24906 A1 of AZL, (University of Western Australia Exhibit 2134, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-43.)	
	NPL625	WO 2004/083432 (the published AZL PCT Application, "Van Ommen"), Pages 71, Exhibit Number 1003 filed in Interference 106,013 on February 17, 2015.	
	NPL626	WO 2013/112053 A1, (University of Western Australia Exhibit 2130, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-177).	
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	First Named Inventor	WILTON, Stephen
	Art Unit	1635
	Examiner Name	K. Chong
	Attorney Docket Number	4140.01500B1

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*		Application Number	16/112,453
		Filing Date	August 24, 2018
		First Named Inventor	Stephen Donald WILTON
		Art Unit	1635
		Examiner Name	Chong, Kimberly
Sheet	1 of 1	Attorney Docket Number	4140.01500B1

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
	NPL709	Office Action mailed July 12, 2018, in United States Patent Application No. 15/645,842, Wilton et al., filed July 10, 2017, 19 pages	
	NPL710	Office Action mailed July 31, 2018, in United States Patent Application No. 15/655,646, Wilton et al., filed July 20, 2017, 15 pages	
	NPL711	Office Action mailed September 7, 2018, in United States Patent Application No. 15/673,019, Wilton et al., filed August 9, 2017, 9 pages	
	NPL712	KOENIG, M., et al., "Alternative splicing of human dystrophin mRNA generates isoforms at the carboxy terminus," Letters to Nature 338:509-511, Nature Publishing Group, United Kingdom (1989)	
	NPL713	TAKESHIMA, Y., et al., "Modulation of in vitro splicing of the upstream intron by modifying an intra-exon sequence which is deleted from the dystrophin gene in dystrophin Kobe," The Journal of Clinical Investigation 95:515-520, The American Society for Clinical Investigation (United States) (1995)	
	NPL714	Office Action mailed October 18, 2018, in United States Patent Application No. 16/112,371, Wilton et al., filed August 24, 2018, 6 pages	

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ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

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APPLICATION NUMBER: *13/741,150*
FILING DATE: *January 14, 2013*

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ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application No. 13/168,857, filed June 24, 2011, now pending, which application is a continuation of U.S. Patent Application No. 12/837,359, filed July 15, 2010, now issued as U.S. Patent No. 8,232,384, which application is a continuation of U.S. Patent Application No. 11/570,691, filed January 15, 2008, now issued as U.S. Patent No. 7,807,816, which application is a 35 U.S.C. § 371 National Phase Application of PCT/AU2005/000943, filed June 28, 2005, which claims priority to Australian Patent Application No. 2004903474, filed June 28, 2004; which applications are each incorporated herein by reference in their entireties.

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with the application is provided in text format in liew of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is SequenceListing.txt. The text file is 61 Kilobytes, was created on January 14, 2013 and is being submitted electronically via EFS-Web.

FIELD OF THE INVENTION

The present invention relates to novel antisense compounds and compositions suitable for facilitating exon skipping. It also provides methods for inducing exon skipping using the novel antisense compounds as well as therapeutic compositions adapted for use in the methods of the invention..

BACKGROUND ART

Significant effort is currently being expended researching methods for suppressing or compensating for disease-causing mutations in genes. Antisense

technologies are being developed using a range of chemistries to affect gene expression at a variety of different levels (transcription, splicing, stability, translation). Much of that research has focused on the use of antisense compounds to correct or compensate for abnormal or disease-associated genes in a myriad of different conditions.

Antisense molecules are able to inhibit gene expression with exquisite specificity and because of this many research efforts concerning oligonucleotides as modulators of gene expression have focused on inhibiting the expression of targeted genes such as oncogenes or viral genes. The antisense oligonucleotides are directed either against RNA (sense strand) or against DNA where they form triplex structures inhibiting transcription by RNA polymerase II. To achieve a desired effect in specific gene down-regulation, the oligonucleotides must either promote the decay of the targeted mRNA or block translation of that mRNA, thereby effectively preventing *de novo* synthesis of the undesirable target protein.

Such techniques are not useful where the object is to up-regulate production of the native protein or compensate for mutations which induce premature termination of translation such as nonsense or frame-shifting mutations. Furthermore, in cases where a normally functional protein is prematurely terminated because of mutations therein, a means for restoring some functional protein production through antisense technology has been shown to be possible through intervention during the splicing processes (Sierakowska H, *et al.*, (1996) Proc Natl Acad Sci USA 93, 12840-12844; Wilton SD, *et al.*, (1999) Neuromusc Disorders 9, 330-338; van Deutekom JC *et al.*, (2001) Human Mol Genet 10, 1547-1554). In these cases, the defective gene transcript should not be subjected to targeted degradation so the antisense oligonucleotide chemistry should not promote target mRNA decay.

In a variety of genetic diseases, the effects of mutations on the eventual expression of a gene can be modulated through a process of targeted exon skipping during the splicing process. The splicing process is directed by complex multi-particle machinery that brings adjacent exon-intron junctions in pre-mRNA into close proximity and performs cleavage of phosphodiester bonds at the ends of the introns with their subsequent

reformation between exons that are to be spliced together. This complex and highly precise process is mediated by sequence motifs in the pre-mRNA that are relatively short semi-conserved RNA segments to which bind the various nuclear splicing factors that are then involved in the splicing reactions. By changing the way the splicing machinery reads or recognises the motifs involved in pre-mRNA processing, it is possible to create differentially spliced mRNA molecules. It has now been recognised that the majority of human genes are alternatively spliced during normal gene expression, although the mechanisms invoked have not been identified. Using antisense oligonucleotides, it has been shown that errors and deficiencies in a coded mRNA could be bypassed or removed from the mature gene transcripts.

In nature, the extent of genetic deletion or exon skipping in the splicing process is not fully understood, although many instances have been documented to occur, generally at very low levels (Sherrat TG, *et al.*, (1993) Am J Hum Genet 53, 1007-1015). However, it is recognised that if exons associated with disease-causing mutations can be specifically deleted from some genes, a shortened protein product can sometimes be produced that has similar biological properties of the native protein or has sufficient biological activity to ameliorate the disease caused by mutations associated with the target exon (Lu QL, *et al.*, (2003) Nature Medicine 9, 1009-1014; Aartsma-Rus A *et al.*, (2004) Am J Hum Genet 74: 83-92).

This process of targeted exon skipping is likely to be particularly useful in long genes where there are many exons and introns, where there is redundancy in the genetic constitution of the exons or where a protein is able to function without one or more particular exons (*e.g.* with the dystrophin gene, which consists of 79 exons; or possibly some collagen genes which encode for repeated blocks of sequence or the huge nebulin or titin genes which are comprised of ~80 and over 370 exons, respectively).

Efforts to redirect gene processing for the treatment of genetic diseases associated with truncations caused by mutations in various genes have focused on the use of antisense oligonucleotides that either: (1) fully or partially overlap with the elements involved in the splicing process; or (2) bind to the pre-mRNA at a position sufficiently

close to the element to disrupt the binding and function of the splicing factors that would normally mediate a particular splicing reaction which occurs at that element (*e.g.*, binds to the pre-mRNA at a position within 3, 6, or 9 nucleotides of the element to be blocked).

For example, modulation of mutant dystrophin pre-mRNA splicing with antisense oligoribonucleotides has been reported both *in vitro* and *in vivo*. In one type of dystrophin mutation reported in Japan, a 52-base pair deletion mutation causes exon 19 to be removed with the flanking introns during the splicing process (Matsuo *et al*., (1991) J Clin Invest., 87:2127-2131). An *in vitro* minigene splicing system has been used to show that a 31-mer 2'-O-methyl oligoribonucleotide complementary to the 5' half of the deleted sequence in dystrophin Kobe exon 19 inhibited splicing of wild-type *pre-mRNA* (Takeshima *et al*. (1995), J. Clin. Invest., 95, 515-520). The same oligonucleotide was used to induce exon skipping from the native dystrophin gene transcript in human cultured lymphoblastoid cells.

Dunckley *et al*., (1997) Nucleosides & Nucleotides, 16, 1665-1668 described *in vitro* constructs for analysis of splicing around exon 23 of mutated dystrophin in the *mdx* mouse mutant, a model for muscular dystrophy. Plans to analyse these constructs *in vitro* using 2' modified oligonucleotides targeted to splice sites within and adjacent to mouse dystrophin exon 23 were discussed, though no target sites or sequences were given.

2'-O-methyl oligoribonucleotides were subsequently reported to correct dystrophin deficiency in myoblasts from the *mdx* mouse from this group. An antisense oligonucleotide targeted to the 3' splice site of murine dystrophin intron 22 was reported to cause skipping of the mutant exon as well as several flanking exons and created a novel in-frame dystrophin transcript with a novel internal deletion. This mutated dystrophin was expressed in 1-2% of antisense treated mdx myotubes. Use of other oligonucleotide modifications such as 2'-O-methoxyethyl phosphodiesters are described (Dunckley *et al*. (1998) Human Mol. Genetics, 5, 1083-90).

Thus, antisense molecules may provide a tool in the treatment of genetic disorders such as Duchenne Muscular Dystrophy (DMD). However, attempts to induce

exon skipping using antisense molecules have had mixed success. Studies on dystrophin exon 19, where successful skipping of that exon from the dystrophin pre-mRNA was achieved using a variety of antisense molecules directed at the flanking splice sites or motifs within the exon involved in exon definition as described by Errington *et al.* (2003) J Gen Med 5, 518-527".

In contrast to the apparent ease of exon 19 skipping, the first report of exon 23 skipping in the *mdx* mouse by Dunckley *et al.*, (1998) is now considered to be reporting only a naturally occurring revertant transcript or artefact rather than any true antisense activity. In addition to not consistently generating transcripts missing exon 23, Dunckley *et al.*, (1998) did not show any time course of induced exon skipping, or even titration of antisense oligonucleotides, to demonstrate dose dependent effects where the levels of exon skipping corresponded with increasing or decreasing amounts of antisense oligonucleotide. Furthermore, this work could not be replicated by other researchers.

The first example of specific and reproducible exon skipping in the *mdx* mouse model was reported by Wilton *et al.*, (1999) Neuromuscular Disorders 9, 330-338. By directing an antisense molecule to the donor splice site, consistent and efficient exon 23 skipping was induced in the dystrophin mRNA within 6 hours of treatment of the cultured cells. Wilton *et al*, (1999), also describe targeting the acceptor region of the mouse dystrophin pre-mRNA with longer antisense oligonucleotides and being unable to repeat the published results of Dunckley *et al.*, (1998). No exon skipping, either 23 alone or multiple removal of several flanking exons, could be reproducibly detected using a selection of antisense oligonucleotides directed at the acceptor splice site of intron 22.

While the first antisense oligonucleotide directed at the intron 23 donor splice site induced consistent exon skipping in primary cultured myoblasts, this compound was found to be much less efficient in immortalized cell cultures expressing higher levels of dystrophin. However, with refined targeting and antisense oligonucleotide design, the efficiency of specific exon removal was increased by almost an order of magnitude (see Mann CJ *et al.*, (2002) J Gen Med 4, 644-654).

Thus, there remains a need to provide antisense oligonucleotides capable of binding to and modifying the splicing of a target nucleotide sequence. Simply directing the antisense oligonucleotides to motifs presumed to be crucial for splicing is no guarantee of the efficacy of that compound in a therapeutic setting.

SUMMARY OF THE INVENTION

The present invention provides antisense molecule compounds and compositions suitable for binding to RNA motifs involved in the splicing of pre-mRNA that are able to induce specific and efficient exon skipping and a method for their use thereof.

The choice of target selection plays a crucial role in the efficiency of exon skipping and hence its subsequent application of a potential therapy. Simply designing antisense molecules to target regions of pre-mRNA presumed to be involved in splicing is no guarantee of inducing efficient and specific exon skipping. The most obvious or readily defined targets for splicing intervention are the donor and acceptor splice sites although there are less defined or conserved motifs including exonic splicing enhancers, silencing elements and branch points.

The acceptor and donor splice sites have consensus sequences of about 16 and 8 bases respectively (see Figure 1 for schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process).

According to a first aspect, the invention provides antisense molecules capable of binding to a selected target to induce exon skipping.

For example, to induce exon skipping in exons 3 to 8, 10 to 16, 19 to 40, 42 to 44, 46, 47, and 50 to 53 in the Dystrophin gene transcript the antisense molecules are preferably selected from the group listed in Table 1A.

In a further example, it is possible to combine two or more antisense oligonucleotides of the present invention together to induce multiple exon skipping in exons 19-20, and 53. This is a similar concept to targeting of a single exon. A

combination or "cocktail" of antisense oligonucleotides are directed at adjacent exons to induce efficient exon skipping.

In another example, to induce exon skipping in exons 19-20, 31, 34 and 53 it is possible to improve exon skipping of a single exon by joining together two or more antisense oligonucleotide molecules. This concept is termed by the inventor as a "weasel", an example of a cunningly designed antisense oligonucleotide. A similar concept has been described in Aartsma-Rus A *et al.*, (2004) Am J Hum Genet 74: 83-92).

According to a second aspect, the present invention provides antisense molecules selected and or adapted to aid in the prophylactic or therapeutic treatment of a genetic disorder comprising at least an antisense molecule in a form suitable for delivery to a patient.

According to a third aspect, the invention provides a method for treating a patient suffering from a genetic disease wherein there is a mutation in a gene encoding a particular protein and the affect of the mutation can be abrogated by exon skipping, comprising the steps of: (a) selecting an antisense molecule in accordance with the methods described herein; and (b) administering the molecule to a patient in need of such treatment.

The invention also addresses the use of purified and isolated antisense oligonucleotides of the invention, for the manufacture of a medicament for treatment of a genetic disease.

The invention further provides a method of treating a condition characterised by Duchenne muscular dystrophy, which method comprises administering to a patient in need of treatment an effective amount of an appropriately designed antisense oligonucleotide of the invention, relevant to the particular genetic lesion in that patient. Further, the invention provides a method for prophylactically treating a patient to prevent or at least minimise Duchene muscular dystrophy, comprising the step of: administering to the patient an effective amount of an antisense oligonucleotide or a pharmaceutical composition comprising one or more of these biological molecules.

The invention also provides kits for treating a genetic disease, which kits comprise at least a antisense oligonucleotide of the present invention, packaged in a suitable container and instructions for its use.

Other aspects and advantages of the invention will become apparent to those skilled in the art from a review of the ensuing description, which proceeds with reference to the following figures.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 Schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process (SEQ ID NOS: 213 and 214).

Figure 2. Diagrammatic representation of the concept of antisense oligonucleotide induced exon skipping to by-pass disease-causing mutations (not drawn to scale). The hatched box represents an exon carrying a mutation that prevents the translation of the rest of the mRNA into a protein. The solid black bar represents an antisense oligonucleotide that prevents inclusion of that exon in the mature mRNA.

Figure 3 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. The preferred compound [H8A(-06+18)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured normal human muscle cells. The less preferred antisense oligonucleotide [H8A(-06+14)] also induces efficient exon skipping, but at much higher concentrations. Other antisense oligonucleotides directed at exon 8 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

Figure 4 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at internal domains within exon 7, presumably exon splicing enhancers. The preferred compound [H7A(+45+67)] induces strong and consistent exon skipping at a transfection concentration of 20

nanomolar in cultured human muscle cells. The less preferred antisense oligonucleotide [H7A(+2+26)] induces only low levels of exon skipping at the higher transfection concentrations. Other antisense oligonucleotides directed at exon 7 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

Figure 5 Gel electrophoresis showing an example of low efficiency exon 6 skipping using two non-preferred antisense molecules directed at human exon 6 donor splice site. Levels of induced exon 6 skipping are either very low [H6D(+04-21)] or almost undetectable [H6D(+18-04)]. These are examples of non-preferred antisense oligonucleotides to demonstrate that antisense oligonucleotide design plays a crucial role in the efficacy of these compounds.

Figure 6 Gel electrophoresis showing strong and efficient human exon 6 skipping using an antisense molecules [H6A(+69+91)] directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells.

Figure 7 Gel electrophoresis showing strong human exon 4 skipping using an antisense molecule H4A(+13+32) directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells,

Figure 8 Gel electrophoresis showing (8B) strong human exon 11 skipping using antisense molecule H11A(+75+97) directed at an exon 11 internal domain; and (8B) strong human exon 12 skipping using antisense molecule H12A(+52+75) directed at exon 12 internal domain.

Figure 9 Gel electrophoresis showing (9A) strong human exon 15 skipping using antisense molecules H15A(+48+71) and H15A(-12+19) directed at an exon

15 internal domain; and (9B) strong human exon 16 skipping using antisense molecules H16A(-12+19) and H16A(-06+25).

Figure 10 Gel electrophoresis showing human exon 19/20 skipping using antisense molecules H20A(+44+71) and H20A(+149+170) directed at an exon 20 and a "cocktail" of antisense oligonucleotides H19A(+35+65, H20A(+44+71) and H20A(+149+170) directed at exons 19/20.

Figure 11 Gel electrophoresis showing human exon 19/20 skipping using "weasels" directed at exons 19 and 20.

Figure 12 Gel electrophoresis showing exon 22 skipping using antisense molecules H22A(+125+106), H22A(+47+69), H22A(+80+101) and H22D(+13-11) directed at exon 22.

Figure 13 Gel electrophoresis showing exon 31 skipping using antisense molecules H31D(+01-25) and H31D(+03-22); and a "cocktail" of antisense molecules directed at exon 31.

Figure 14 Gel electrophoresis showing exon 33 skipping using antisense molecules H33A(+30+56) and H33A(+64+88) directed at exon 33.

Figure 15 Gel electrophoresis showing exon 35 skipping using antisense molecules H35A(+141+161), H35A(+116+135), and H35A(+24+43) and a "cocktail of two antisense molecules, directed at exon 35.

Figure 16 Gel electrophoresis showing exon 36 skipping using antisense molecules H32A(+49+73) and H36A(+26+50) directed at exon 36.

Figure 17 Gel electrophoresis showing exon 37 skipping using antisense molecules H37A(+82+105) and H37A(+134+157) directed at exon 37.

Figure 18 Gel electrophoresis showing exon 38 skipping using antisense molecule H38A(+88+112) directed at exon 38.

Figure 19 Gel electrophoresis showing exon 40 skipping using antisense molecule H40A(-05+17) directed at exon 40.

Figure 20 Gel electrophoresis showing exon 42 skipping using antisense molecule H42A(-04+23) directed at exon 42.

Figure 21 Gel electrophoresis showing exon 46 skipping using antisense molecule H46A(+86+115) directed a# exon 46

Figure 22 Gel electrophoresis showing exon 51, exon 52 and exon 53 skipping using various antisense molecules directed at exons 51, 52 and 53, respectively. A "cocktail" of antisense molecules is also shown directed at exon 53.

BRIEF DESCRIPTION OF THE SEQUENCE LISTINGS

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
1	H8A(-06+18)	GAU AGG UGG UAU CAA CAU CUG UAA
2	H8A (-03+18)	GAU AGG UGG UAU CAA CAU CUG
3	H8A(-07+18)	GAU AGG UGG UAU CAA CAU CUG UAA G
4	H8A(-06+14)	GGU GGU AUC AAC AUC UGU AA
5	H8A(-10+10)	GUA UCA ACA UCU GUA AGC AC
6	H7A(+45+67)	UGC AUG UUC CAG UCG UUG UGU GG
7	H7A(+02+26)	CAC UAU UCC AGU CAA AUA GGU CUG G
8	H7D(+15-10)	AUU UAC CAA CCU UCA GGA UCG AGU A
9	H7A(-18+03)	GGC CUA AAA CAC AUA CAC AUA
10	C6A(-10+10)	CAU UUU UGA CCU ACA UGU GG
11	C6A(-14+06)	UUU GAC CUA CAU GUG GAA AG
12	C6A(-14+12)	UAC AUU UUU GAC CUA CAU GUG GAA AG
13	C6A(-13+09)	AUU UUU GAC CUA CAU GGG AAA G
14	CH6A(+69+91)	UAC GAG UUG AUU GUC GGA CCC AG
15	C6D(+12-13)	GUG GUC UCC UUA CCU AUG ACU GUG G
16	C6D(+06-11)	GGU CUC CUU ACC UAU GA
17	H6D(+04-21)	UGU CUC AGU AAU CUU CUU ACC UAU
18	H6D(+18-04)	UCU UAC CUA UGA CUA UGG AUG AGA
19	H4A(+13+32)	GCA UGA ACU CUU GUG GAU CC
20	H4D(+04-16)	CCA GGG UAC UAC UUA CAU UA
21	H4D(-24-44)	AUC GUG UGU CAC AGC AUC CAG
22	H4A(+11+40)	UGU UCA GGG CAU GAA CUC UUG UGG AUC CUU
23	H3A(+30+60)	UAG GAG GCG CCU CCC AUC CUG UAG GUC ACU G
24	H3A(+35+65)	AGG UCU AGG AGG CGC CUC CCA UCC UGU AGG U
25	H3A(+30+54)	GCG CCU CCC AUC CUG UAG GUC ACU G
26	H3D(+46-21)	CUU CGA GGA GGU CUA GGA GGC GCC UC
27	H3A(+30+50)	CUC CCA UCC UGU AGG UCA CUG

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
28	H3D(+19-03)	UAC CAG UUU UUG CCC UGU CAG G
29	H3A(-06+20)	UCA AUA UGC UGC UUC CCA AAC UGA AA
30	H3A(+37+61)	CUA GGA GGC GCC UCC CAU CCU GUA G
31	H5A(+20+50)	UUA UGA UUU CCA UCU ACG AUG UCA GUA CUU C
32	H5D(+25-05)	CUU ACC UGC CAG UGG AGG AUU AUA UUC CAA A
33	H5D(+10-15)	CAU CAG GAU UCU UAC CUG CCA GUG G
34	H5A(+10+34)	CGA UGU CAG UAC UUC CAA UAU UCA C
35	H5D(-04-21)	ACC AUU CAU CAG GAU UCU
36	H5D(+16-02)	ACC UGC CAG UGG AGG AUU
37	H5A(-07+20)	CCA AUA UUC ACU AAA UCA ACC UGU UAA
38	H5D(+18-12)	CAG GAU UGU UAC CUG CCA GUG GAG GAU UAU
39	H5A(+05+35)	ACG AUG UCA GUA CUU CCA AUA UUC ACU AAA U
40	H5A(+15+45)	AUU UCC AUC UAC GAU GUC AGU ACU UCC AAU A
41	H10A(-05+16)	CAG GAG CUU CCA AAU GCU GCA
42	H10A(-05+24)	CUU GUC UUC AGG AGC UUC CAA AUG CUG CA
43	H10A(+98+119)	UCC UCA GCA GAA AGA AGC CAC G
44	H10A(+130+149)	UUA GAA AUC UCU CCU UGU GC
45	H10A(-33-14)	UAA AUU GGG UGU UAC ACA AU
46	H11D(+26+49)	CCC UGA GGC AUU CCC AUC UUG AAU
47	H11D(+11-09)	AGG ACU UAC UUG CUU UGU UU
48	H11A(+118+140)	CUU GAA UUU AGG AGA UUC AUC UG
49	H11A(+75+97)	CAU CUU CUG AUA AUU UUC CUG UU
50	H12A(+52+75)	UCU UCU GUU UUU GUU AGC CAG UCA
51	H12A(-10+10)	UCU AUG UAA ACU GAA AAU UU
52	H12A(+11+30)	UUC UGG AGA UCC AUU AAA AC
53	H13A(+77+100)	CAG CAG UUG CGU GAU CUC CAC UAG
54	H13A(+55+75)	UUC AUC AAC UAC CAC CAC CAU
55	H13D(+06-19)	CUA AGC AAA AUA AUC UGA CCU UAA G
56	H14A(+37+64)	CUU GUA AAA GAA CCC AGC GGU CUU CUG U
57	H14A(+14+35)	CAU CUA CAG AUG UUU GCC CAU C
58	H14A(+51+73)	GAA GGA UGU CUU GUA AAA GAA CC
59	H14D(-02+18)	ACC UGU UCU UCA GUA AGA CG
60	H14D(+14-10)	CAU GAC ACA CCU GUU CUU CAG UAA
61	H14A(+61+80)	CAU UUG AGA AGG AUG UCU UG
62	H14A(-12+12)	AUC UCC CAA UAC CUG GAG AAG AGA
63	H15A(-12+19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
		CAU U
64	H15A(+48+71)	UCU UUA AAG CCA GUU GUG UGA AUC
65	H15A(+08+28)	UUU CUG AAA GCC AUG CAC UAA
66	H15D(+17-08)	GUA CAU ACG GCC AGU UUU UGA AGA C
67	H16A(-12+19)	CUA GAU CCG CUU UUA AAA CCU GUU AAA ACA A
68	H16A(-06+25)	UCU UUU CUA GAU CCG CUU UUA AAA CCU GUU A
69	H16A(-06+19)	CUA GAU CCG CUU UUA AAA CCU GUU A
70	H16A(+87+109)	CCG UCU UCU GGG UCA CUG ACU UA
71	H16A(-07+19)	CUA GAU CCG CUU UUA AAA CCU GUU AA
72	H16A(-07+13)	CCG CUU UUA AAA CCU GUU AA
73	H16A(+12+37)	UGG AUU GCU UUU UCU UUU CUA GAU CC
74	H16A(+92+116)	CAU GCU UCC GUC UUC UGG GUC ACU G
75	H16A(+45+67)	G AUC UUG UUU GAG UGA AUA CAG U
76	H16A(+105+126)	GUU AUC CAG CCA UGC UUC CGU C
77	H16D(+05-20)	UGA UAA UUG GUA UCA CUA ACC UGU G
78	H16D(+12-11)	GUA UCA CUA ACC UGU GCU GUA C
79	H19A(+35+53)	CUG CUG GCA UCU UGC AGU U
80	H19A(+35+65)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U
81	H20A(+44+71)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C
82	H20A(+147+168)	CAG CAG UAG UUG UCA UCU GCU C
83	H20A(+185+203)	UGA UGG GGU GGU GGG UUG G
84	H20A(-08+17)	AUC UGC AUU AAC ACC CUC UAG AAA G
85	H20A(+30+53)	CCG GCU GUU CAG UUG UUC UGA GGC
86	H20A(-11+17)	AUC UGC AUU AAC ACC CUC UAG AAA GAA A
87	H20D(+08-20)	GAA GGA GAA GAG AUU CUU ACC UUA CAA A
88	H20A(+44+63)	AUU CGA UCC ACC GGC UGU UC
89	H20A(+149+168	CAG CAG UAG UUG UCA UCU GC
90	H21A(-06+16)	GCC GGU UGA CUU CAU CCU GUG C
91	H21A(+85+106)	CUG CAU CCA GGA ACA UGG GUC C
92	H21A(+85+108)	GUC UGC AUC CAG GAA CAU GGG UC
93	H21A(+08+31)	GUU GAA GAU CUG AUA GCC GGU UGA
94	H21D(+18-07)	UAC UUA CUG UCU GUA GCU CUU UCU
95	H22A(+22+45)	CAC UCA UGG UCU CCU GAU AGC GCA
96	H22A(+125+106)	CUG CAA UUC CCC GAG UCU CUG C
97	H22A(+47+69)	ACU GCU GGA CCC AUG UCC UGA UG
98	H22A(+80+101)	CUA AGU UGA GGU AUG GAG AGU
99	H22D(+13-11)	UAU UCA CAG ACC UGC AAU UCC CC
100	H23A(+34+59)	ACA GUG GUG CUG AGA UAG UAU AGG CC

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
101	H23A(+18+39)	UAG GCC ACU UUG UUG CUC UUG C
102	H23A(+72+90)	UUC AGA GGG CGC UUU CUU C
103	H24A(+48+70)	GGG CAG GCC AUU CCU CCU UCA GA
104	H24A(-02+22)	UCU UCA GGG UUU GUA UGU GAU UCU
105	H25A(+9+36)	CUG GGC UGA AUU GUC UGA AUA UCA CUG
106	H25A(+131+156)	CUG UUG GCA CAU GUG AUC CCA CUG AG
107	H25D(+16-08)	GUC UAU ACC UGU UGG CAC AUG UGA
108	H26A(+132+156)	UGC UUU CUG UAA UUC AUC UGG AGU U
109	H26A(-07+19)	CCU CCU UUC UGG CAU AGA CCU UCC AC
110	H26A(+68+92)	UGU GUC AUC CAU UCG UGC AUC UCU G
111	H27A(+82+106)	UUA AGG CCU CUU GUG CUA CAG GUG G
112	H27A(-4+19)	GGG GCU CUU CUU UAG CUC UCU GA
113	H27D(+19-03)	GAC UUC CAA AGU CUU GCA UUU C
114	H28A(-05+19)	GCC AAC AUG CCC AAA CUU CCU AAG
115	H28A(+99+124)	CAG AGA UUU CCU CAG CUC CGC CAG GA
116	H28D(+16-05)	CUU ACA UCU AGC ACC UCA GAG
117	H29A(+57+81)	UCC GCC AUC UGU UAG GGU CUG UGC C
118	H29A(+18+42)	AUU UGG GUU AUC CUC UGA AUG UCG C
119	H29D(+17-05)	CAU ACC UCU UCA UGU AGU UCC C
120	H30A(+122+147)	CAU UUG AGC UGC GUC CAC CUU GUC UG
121	H30A(+25+50)	UCC UGG GCA GAC UGG AUG CUC UGU UC
122	H30D(+19-04)	UUG CCU GGG CUU CCU GAG GCA UU
123	H31D(+06-18)	UUC UGA AAU AAC AUA UAC CUG UGC
124	H31D(+03-22)	UAG UUU CUG AAA UAA CAU AUA CCU G
125	H31A(+05+25)	GAC UUG UCA AAU CAG AUU GGA
126	H31D(+04-20)	GUU UCU GAA AUA ACA UAU ACC UGU
127	H32D(+04-16)	CAC CAG AAA UAC AUA CCA CA
128	H32A(+151+170)	CAA UGA UUU AGC UGU GAC UG
129	H32A(+10+32)	CGA AAC UUC AUG GAG ACA UCU UG
130	H32A(+49+73)	CUU GUA GAC GCU GCU CAA AAU UGG C
131	H33D(+09-11)	CAU GCA CAC ACC UUU GCU CC
132	H33A(+53+76)	UCU GUA CAA UCU GAC GUC CAG UCU
133	H33A(+30+56)	GUC UUU AUC ACC AUU UCC ACU UCA GAC
134	H33A(+64+88)	CCG UCU GCU UUU UCU GUA CAA UCU G
135	H34A(+83+104)	UCC AUA UCU GUA GCU GCC AGC C
136	H34A(+143+165)	CCA GGC AAC UUC AGA AUC CAA AU
137	H34A(-20+10)	UUU CUG UUA CCU GAA AAG AAU UAU AAU GAA
138	H34A(+46+70)	CAU UCA UUU CCU UUC GCA UCU UAC G
139	H34A(+95+120)	UGA UCU CUU UGU CAA UUC CAU AUC UG
140	H34D(+10-20)	UUC AGU GAU AUA GGU UUU ACC UUU CCC

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
		CAG
141	H34A(+72+96)	CUG UAG CUG CCA GCC AUU CUG UCA AG
142	H35A(+141+161)	UCU UCU GCU CGG GAG GUG ACA
143	H35A(+116+135)	CCA GUU ACU AUU CAG AAG AC
144	H35A(+24+43)	UCU UCA GGU GCA CCU UCU GU
145	H36A(+26+50)	UGU GAU GUG GUC CAC AUU CUG GUC A
146	H36A(-02+18)	CCA UGU GUU UCU GGU AUU CC
147	H37A(+26+50)	CGU GUA GAG UCC ACC UUU GGG CGU A
148	H37A(+82+105)	UAC UAA UUU CCU GCA GUG GUC ACC
149	H37A(+134+157)	UUC UGU GUG AAA UGG CUG CAA AUC
150	H38A(-01+19)	CCU UCA AAG GAA UGG AGG CC
151	H38A(+59+83)	UGC UGA AUU UCA GCC UCC AGU GGU U
152	H38A(+88+112)	UGA AGU CUU CCU CUU UCA GAU UCA C
153	H39A(+62+85)	CUG GCU UUC UCU CAU CUG UGA UUC
154	H39A(+39+58)	GUU GUA AGU UGU CUC CUC UU
155	H39A(+102+121)	UUG UCU GUA ACA GCU GCU GU
156	H39D(+10-10)	GCU CUA AUA CCU UGA GAG CA
157	H40A(-05+17)	CUU UGA GAC CUC AAA UCC UGU U
158	H40A(+129+153)	CUU UAU UUU CCU UUC AUC UCU GGG C
159	H42A(-04+23)	AUC GUU UCU UCA CGG ACA GUG UGC UGG
160	H42A(+86+109)	GGG CUU GUG AGA CAU GAG UGA UUU
161	H42D(+19-02)	A CCU UCA GAG GAC UCC UCU UGC
162	H43D(+10-15)	UAU GUG UUA CCU ACC CUU GUC GGU C
163	H43A(+101+120)	GGA GAG AGC UUC CUG UAG CU
164	H43A(+78+100)	UCA CCC UUU CCA CAG GCG UUG CA
165	H44A(+85+104)	UUU GUG UCU UUC UGA GAA AC
166	H44D(+10-10)	AAA GAC UUA CCU UAA GAU AC
167	H44A(-06+14)	AUC UGU CAA AUC GCC UGC AG
168	H46D(+16-04)	UUA CCU UGA CUU GCU CAA GC
169	H46A(+90+109)	UCC AGG UUC AAG UGG GAU AC
170	H47A(+76+100)	GCU CUU CUG GGC UUA UGG GAG CAC U
171	H47D(+25-02)	ACC UUU AUC CAC UGG AGA UUU GUC UGC
172	H47A(-9+12)	UUC CAC CAG UAA CUG AAA CAG
173	H50A(+02+30)	CCA CUC AGA GCU CAG AUC UUC UAA CUU CC
174	H50A(+07+33)	CUU CCA CUC AGA GCU CAG AUC UUC UAA
175	H50D(+07-18)	GGG AUC CAG UAU ACU UAC AGG CUC C
176	H51A(-01+25)	ACC AGA GUA ACA GUC UGA GUA GGA GC
177	H51D(+16-07)	CUC AUA CCU UCU GCU UGA UGA UC
178	H51A(+111 +134)	UUC UGU CCA AGC CCG GUU GAA AUC
179	H51A(+61+90)	ACA UCA AGG AAG AUG GCA UUU CUA GUU UGG

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5' - 3')
180	H51A(+66+90)	ACA UCA AGG AAG AUG GCA UUU CUA G
181	H51A(+66+95)	CUC CAA CAU CAA GGA AGA UGG CAU UUC UAG
182	H51D(+08-17)	AUC AUU UUU UCU CAU ACC UUC UGC U
183	H51A/D(+08-17) & (-15+)	AUC AUU UUU UCU CAU ACC UUC UGC UAG GAG CUA AAA
184	H51A(+175+195)	CAC CCA CCA UCA CCC UCU GUG
185	H51A(+199+220)	AUC AUC UCG UUG AUA UCC UCA A
186	H52A(-07+14)	UCC UGC AUU GUU GCC UGU AAG
187	H52A(+12+41)	UCC AAC UGG GGA CGC CUC UGU UCC AAA UCC
188	H52A(+17+37)	ACU GGG GAC GCC UCU GUU CCA
189	H52A(+93+112)	CCG UAA UGA UUG UUC UAG CC
190	H52D(+05-15)	UGU UAA AAA ACU UAC UUC GA
191	H53A(+45+69)	CAU UCA ACU GUU GCC UCC GGU UCU G
192	H53A(+39+62)	CUG UUG CCU CCG GUU CUG AAG GUG
193	H53A(+39+69)	CAU UCA ACU GUU GCC UCC GGU UCU GAA GGU G
194	H53D(+14-07)	UAC UAA CCU UGG UUU CUG UGA
195	H53A(+23+47)	CUG AAG GUG UUC UUG UAC UUC AUC C
196	H53A(+150+176)	UGU AUA GGG ACC CUC CUU CCA UGA CUC
197	H53D(+20-05)	CUA ACC UUG GUU UCU GUG AUU UUC U
198	H53D(+09-18)	GGU AUC UUU GAU ACU AAC CUU GGU UUC
199	H53A(-12+10)	AUU CUU UCA ACU AGA AUA AAA G
200	H53A(-07+18)	GAU UCU GAA UUC UUU CAA CUA GAA U
201	H53A(+07+26)	AUC CCA CUG AUU CUG AAU UC
202	H53A(+124+145)	UUG GCU CUG GCC UGU CCU AAG A
203	H46A(+86+115)	CUC UUU UCC AGG UUC AAG UGG GAU ACU AGC
204	H46A(+107+137)	CAA GCU UUU CUU UUA GUU GCU GCU CUU UUC C
205	H46A(-10+20)	UAU UCU UUU GUU CUU CUA GCC UGG AGA AAG
206	H46A(+50+77)	CUG CUU CCU CCA ACC AUA AAA CAA AUU C
207	H45A(-06+20)	CCA AUG CCA UCC UGG AGU UCC UGU AA
208	H45A(+91 +110)	UCC UGU AGA AUA CUG GCA UC
209	H45A(+125+151)	UGC AGA CCU CCU GCC ACC GCA GAU UCA
210	H45D(+16 -04)	CUA CCU CUU UUU UCU GUC UG
211	H45A(+71+90)	UGU UUU UGA GGA UUG CUG AA

Table 1A: Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
81 82	H20A(+44+71) H20A(+147+168)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C CAG CAG UAG UUG UCA UCU GCU C
80 81 82	H19A(+35+65) H20A(+44+71) H20A(+147+168)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U CUG GCA GAA UUC GAU CCA CCG GCU GUU C CAG CAG UAG UUG UCA UCU GCU C
194 195 196	H53D(+14-07) H53A(+23+47) H53A(+150+175)	UAC UAA CCU UGG UUU CUG UGA CUG AAG GUG UUC UUG UAC UUC AUC C UGU AUA GGG ACC CUC CUU CCA UGA CUC

Table 1B: Description of a cocktail of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
81 82	H20A(+44+71)- H20A(+147+168)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C- CAG CAG UAG UUG UCA UCU GCU C
80 88 79	H19A(+35+65)- H20A(+44+63)- H20A(+149+168)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U -AUU CGA UCC ACC GGC UGU UC- CUG CUG GCA UCU UGC AGU U
80 88	H19A(+35+65)- H20A(+44+63)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U -AUU CGA UCC ACC GGC UGU UC-
80 79	H19A(+35+65)- H20A(+149+168)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U -CUG CUG GCA UCU UGC AGU U
138 139	H34A(+46+70)- H34A(+94+120)	CAU UCA UUU CCU UUC GCA UCU UAC G- UGA UCU CUU UGU CAA UUC CAU AUC UG

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
124 144	H31D(+03-22)- UU- H35A(+24+43)	UAG UUU CUG AAA UAA CAU AUA CCU G- UU- UCU UCA GGU GCA CCU UCU GU
195 196 194	H53A(+23+47)- AA- H53A(+150+175)- AA- H53D(+14-07)	CUG AAG GUG UUC UUG UAC UUC AUC C- UGU AUA GGG ACC CUC CUU CCA UGA CUC- AA- UAC UAA CCU UGG UUU CUG UGA
- 212	Aimed at exons 19/20/20	CAG CAG UAG UUG UCA UCU GCU CAA CUG GCA GAA UUC GAU CCA CCG GCU GUU CAA GCC UGA GCU GAU CUG CUC GCA UCU UGC AGU

Table 1C: Description of a "weasel" of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

DETAILED DESCRIPTION OF THE INVENTION

General

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variation and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally equivalent products, compositions and methods are clearly within the scope of the invention as described herein.

Sequence identity numbers (SEQ ID NO:) containing nucleotide and amino acid sequence information included in this specification are collected at the end of the description and have been prepared using the programme Patentln Version 3.0. Each

nucleotide or amino acid sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (*e.g.* <210>1, <210>2, etc.). The length, type of sequence and source organism for each nucleotide or amino acid sequence are indicated by information provided in the numeric indicator fields <211>, <212> and <213>, respectively. Nucleotide and amino acid sequences referred to in the specification are defined by the information provided in numeric indicator field <400> followed by the sequence identifier (*e.g.* <400>1, <400>2, etc.).

An antisense molecules nomenclature system was proposed and published to distinguish between the different antisense molecules (see Mann *et al.*, (2002) J Gen Med 4, 644-654). This nomenclature became especially relevant when testing several slightly different antisense molecules, all directed at the same target region, as shown below:

H # A/D (x : y).

The first letter designates the species (*e.g.* H: human, M: rnurine, C: canine) "#" designates target dystrophin exon number.

"A/D" indicates acceptor or donor splice site at the beginning and end of the exon, respectively.

(x y) represents the annealing coordinates where "-" or "+" indicate intronic or exonic sequences respectively. As an example, A(-6+18) would indicate the last 6 bases of the intron preceding the target exon and the first 18 bases of the target exon. The closest splice site would be the acceptor so these coordinates would be preceded with an "A". Describing annealing coordinates at the donor splice site could be D(+2-18) where the last 2 exonic bases and the first 18 intronic bases correspond to the annealing site of the antisense molecule. Entirely exonic annealing coordinates that would be represented by A(+65+85), that is the site between the 65th and 85th nucleotide from the start of that exon.

The entire disclosures of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference. No admission is made that any of the references

constitute prior art or are part of the common general knowledge of those working in the field to which this invention relates.

As used necessarily herein the term "derived" and "derived from" shall be taken to indicate that a specific integer may be obtained from a particular source *albeit* not directly from that source.

Throughout this specification, unless the context requires o#herwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

DESCRIPTION OF THE PREFERRED EMBODIMENT

When antisense molecule(s) are targeted to nucleotide sequences involved in splicing in exons within pre-mRNA sequences, normal splicing of the exon may be inhibited causing the splicing machinery to by-pass the entire mutated exon from the mature mRNA. The concept of antisense oligonucleotide induced exon skipping is shown in Figure 2. In many genes, deletion of an entire exon would lead to the production of a non-functional protein through the loss of important functional domains or the disruption of the reading frame. In some proteins, however, it is possible to shorten the protein by deleting one or more exons, without disrupting the reading frame, from within the protein without seriously altering the biological activity of the protein. Typically, such proteins have a structural role and or possess functional domains at their ends. The present invention describes antisense molecules capable of binding to specified dystrophin pre-mRNA targets and re-directing processing of that gene.

Antisense Molecules

According to a first aspect of the invention, there is provided antisense molecules capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules are preferably selected from the group of compounds shown in Table 1A. There is also provided a combination or "cocktail" of two or more antisense oligonucleotides capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules in a "cocktail" are preferably selected from the group of compounds shown in Table 1B. Alternatively, exon skipping may be induced by antisense oligonucleotides joined together "weasels" preferably selected from the group of compounds shown in Table 1C.

Designing antisense molecules to completely mask consensus splice sites may not necessarily generate any skipping of the targeted exon. Furthermore, the inventors have discovered that size or length of the antisense oligonucleotide itself is not always a primary factor when designing antisense molecules. With some targets such as exon 19, antisense oligonucleotides as short as 12 bases were able to induce exon skipping, *albeit* not as efficiently as longer (20-31 bases) oligonucleotides. In some other targets, such as murine dystrophin exon 23, antisense oligonucleotides only 17 residues long were able to induce more efficient skipping than another overlapping compound of 25 nucleotides.

The inventors have also discovered that there does not appear to be any standard motif that can be blocked or masked by antisense molecules to redirect splicing. In some exons, such as mouse dystrophin exon 23, the donor splice site was the most amenable to target to re-direct skipping of that exon. It should be noted that designing and testing a series of exon 23 specific antisense molecules to anneal to overlapping regions of the donor splice site showed considerable variation in the efficacy of induced exon skipping. As reported in Mann *et al*., (2002) there was a significant variation in the efficiency of bypassing the nonsense mutation depending upon antisense oligonucleotide annealing ("Improved antisense oligonucleotide induced exon skipping in the *mdx* mouse model of muscular dystrophy". J Gen Med 4: 644-654). Targeting the acceptor site of

exon 23 or several internal domains was not found to induce any consistent exon 23 skipping.

In other exons targeted for removal, masking the donor splice site did not induce any exon skipping. However, by directing antisense molecules to the acceptor splice site (human exon 8 as discussed below), strong and sustained exon skipping was induced. It should be noted that removal of human exon 8 was tightly linked with the co-removal of exon 9. There is no strong sequence homology between the exon 8 antisense oligonucleotides and corresponding regions of exon 9 so it does not appear to be a matter of cross reaction. Rather the splicing of these two exons is inextricably linked. This is not an isolated instance as the same effect is observed in canine cells where targeting exon 8 for removal also resulted in the skipping of exon 9. Targeting exon 23 for removal in the mouse dystrophin pre-mRNA also results in the frequent removal of exon 22 as well. This effect occurs in a dose dependent manner and also indicates close coordinated processing of 2 adjacent exons.

In other targeted exons, antisense molecules directed at the donor or acceptor splice sites did not induce exon skipping while annealing antisense molecules to intra-exonic regions (*i.e.* exon splicing enhancers within human dystrophin exon 6) was most efficient at inducing exon skipping. Some exons, both mouse and human exon 19 for example, are readily skipped by targeting antisense molecules to a variety of motifs. That is, targeted exon skipping is induced after using antisense oligonucleotides to mask donor and acceptor splice sites or exon splicing enhancers.

To identify and select antisense oligonucleotides suitable for use in the modulation of exon skipping, a nucleic acid sequence whose function is to be modulated must first be identified. This may be, for example, a gene (or mRNA transcribed form the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (*i.e.* splice donor sites, splice acceptor sites, or exonic splicing enhancer elements). Splicing branch points and exon

recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

Preferably, the present invention aims to provide antisense molecules capable of binding to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping. Duchenne muscular dystrophy arises from mutations that preclude the synthesis of a functional dystrophin gene product. These Duchenne muscular dystrophy gene defects are typically nonsense mutations or genomic rearrangements such as deletions, duplications or micro-deletions or insertions that disrupt the reading frame. As the human dystrophin gene is a large and complex gene with the 79 exons being spliced together to generate a mature mRNA with an open reading frame of approximately 11,000 bases, there are many positions where these mutations can occur. Consequently, a comprehensive antisense oligonucleotide based therapy to address many of the different disease-causing mutations in the dystrophin gene will require that many exons can be targeted for removal during the splicing process.

Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (*i.e.* splice donor sites, splice acceptor sites or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides which can hydrogen bond with each other. Thus, "specifically hybridisable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an antisense molecule need not be 100% complementary to that of its target sequence to be specifically hybridisable. An antisense molecule is specifically hybridisable when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to

non-target sequences under conditions in which specific binding is desired, *i.e.*, under physiological conditions in the case of *in vivo* assays or therapeutic treatment, and in the case of *in vitro* assays, under conditions in which the assays are performed.

While the above method may be used to select antisense molecules capable of deleting any exon from within a protein that is capable of being shortened without affecting its biological function, the exon deletion should not lead to a reading frame shift in the shortened transcribed mRNA. Thus, if in a linear sequence of three exons the end of the first exon encodes two of three nucleotides in a codon and the next exon is deleted then the third exon in the linear sequence must start with a single nucleotide that is capable of completing the nucleotide triplet for a codon. If the third exon does not commence with a single nucleotide there will be a reading frame shift that would lead to the generation of truncated or a non-functional protein.

It wilt be appreciated that the codon arrangements at the end of exons in structural proteins may not always break at the end of a codon, consequently there may be a need to delete more than one exon from the pre-mRNA to ensure in-frame reading of the mRNA. In such circumstances, a plurality of antisense oligonucleotides may need to be selected by the method of the invention wherein each is directed to a different region responsible for inducing splicing in the exons that are to be deleted.

The length of an antisense molecule may vary so long as it is capable of binding selectively to the intended location within the pre-mRNA molecule. The length of such sequences can be determined in accordance with selection procedures described herein. Generally, the antisense molecule will be from about 10 nucleotides in length up to about 50 nucleotides in length. It will be appreciated however that any length of nucleotides within this range may be used in the method. Preferably, the length of the antisense molecule is between 17 to 30 nucleotides in length.

In order to determine which exons can be connected in a dystrophin gene, reference should be made to an exon boundary map. Connection of one exon with another is based on the exons possessing the same number at the 3' border as is present at the 5' border of the exon to which it is being connected. Therefore, if exon 7 were deleted, exon

6 must connect to either exons 12 or 18 to maintain the reading frame. Thus, antisense oligonucleotides would need to be selected which redirected splicing for exons 7 to 11 in the first instance or exons 7 to 17 in the second instance. Another and somewhat simpler approach to restore the reading frame around an exon 7 deletion would be to remove the two flanking exons. Induction of exons 6 and 8 skipping should result in an in-frame transcript with the splicing of exons 5 to 9. In practise however, targeting exon 8 for removal from the pre-mRNA results in the co-removal of exon 9 so the resultant transcript would have exon 5 joined to exon 10. The inclusion or exclusion of exon 9 does not alter the reading frame. Once the antisense molecules to be tested have been identified, they are prepared according to standard techniques known in the art. The most common method for producing antisense molecules is the methylation of the 2' hydroxyribose position and the incorporation of a phosphorothioate backbone produces molecules that superficially resemble RNA but that are much more resistant to nuclease degradation.

To avoid degradation of pre-mRNA during duplex formation with the antisense molecules, the antisense molecules used in the method may be adapted to minimise or prevent cleavage by endogenous RNase H. This property is highly preferred as the treatment of the RNA with the unmethylated oligonucleotides either intracellularly or in crude extracts that contain RNase H leads to degradation of the pre-mRNA: antisense oligonucleotide duplexes. Any form of modified antisense molecules that is capable of by-passing or not inducing such degradation may be used in the present method. An example of antisense molecules which when duplexed with RNA are not cleaved by cellular RNase H is 2'-O-methyl derivatives. 2'-O-methyl-oligoribonucleotides are very stable in a cellular environment and in animal tissues, and their duplexes with RNA have higher Tm values than their ribo- or deoxyribo- counterparts.

Antisense molecules that do not activate RNase H can be made in accordance with known techniques (*see, e.g.*, U.S. Pat. 5,149,797). Such antisense molecules, which may be deoxyribonucleotide or ribonucleotide sequences, simply contain any structural modification which sterically hinders or prevents binding of RNase H to a duplex molecule containing the oligonucleotide as one member thereof, which structural

modification does not substantially hinder or disrupt duplex formation. Because the portions of the oligonucleotide involved in duplex formation are substantially different from those portions involved in RNase H binding thereto, numerous antisense molecules that do not activate RNase H are available. For example, such antisense molecules may be oligonucleotides wherein at least one, or all, of the inter-nucleotide bridging phosphate residues are modified phosphates, such as methyl phosphonates, methyl phosphorothioates, phosphoromorpholidates, phosphoropiperazidates and phosphoramidates. For example, every other one of the internucleotide bridging phosphate residues may be modified as described. In another non-limiting example, such antisense molecules are molecules wherein at least one, or all, of the nucleotides contain a 2' lower alkyl moiety (*e.g.*, C_1-C_4, linear or branched, saturated or unsaturated alkyl, such as methyl, ethyl, ethenyl, propyl, 1-propenyl, 2-propenyl, and isopropyl). For example, every other one of the nucleotides may be modified as described.

While antisense oligonucleotides are a preferred form of the antisense molecules, the present invention comprehends other oligomeric antisense molecules, including but not limited to oligonucleotide mimetics such as are described below.

Specific examples of preferred antisense compounds useful in this invention include oligonucleotides containing modified backbones or non-natural inter-nucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their inter-nucleoside backbone can also be considered to be oligonucleosides.

In other preferred oligonucleotide mimetics, both the sugar and the inter-nucleoside linkage, *i.e.*, the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced

with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleo-bases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone.

Modified oligonucleotides may also contain one or more substituted sugar moieties. Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. Certain nucleo-bases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thioether, *e.g.*, hexyl-S-tritylthiol, a thiocholesterol, an aliphatic chain, *e.g.*, dodecandiol or undecyl residues, a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety.

It is not necessary far all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds that are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this invention, are antisense molecules, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, *i.e.*, a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region

wherein the oligonucleotide is modified so as to confer upon the increased resistance to nuclease degradation, increased cellular uptake, and an additional region for increased binding affinity for the target nucleic acid.

Methods of Manufacturing Antisense Molecules

The antisense molecules used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). One method for synthesising oligonucleotides on a modified solid support is described in U.S. Pat. No. 4,458,066.

Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates ~ and alkylated derivatives. In one such automated embodiment, diethyl-phosphoramidites are used as starting materials and may be synthesized as described by Beaucage, *et al*., (1981) *Tetrahedron Letters*, 22:1859-1862.

The antisense molecules of the invention are synthesised *in vitro* and do not include antisense compositions of biological origin, or genetic vector constructs designed to direct the *in vivo* synthesis of antisense molecules. The molecules of the invention may also be mixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption.

Therapeutic Agents

The present invention also can be used as a prophylactic or therapeutic, which may be utilised for the purpose of treatment of a genetic disease.

Accordingly, in one embodiment the present invention provides antisense molecules that bind to a selected target in the dystrophin pre-mRNA to induce efficient and

consistent exon skipping described herein in a therapeutically effective amount admixed with a pharmaceutically acceptable carrier, diluent, or excipient.

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similarly untoward reaction, such as gastric upset and the like, when administered to a patient. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in Martin, *Remington's Pharmaceutical Sciences*, 18th Ed., Mack Publishing Co., Easton, PA, (1990).

In a more specific form of the invention there are provided pharmaceutical compositions comprising therapeutically effective amounts of an antisense molecule together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (*e.g.*, Tris-HCl, acetate, phosphate), pH and ionic strength and additives such as detergents and solubilizing agents (*e.g.*, Tween 80, Polysorbate 80), anti-oxidants (*e.g.*, ascorbic acid, sodium metabisulfite), preservatives (*e.g.*, Thimersol, benzyl alcohol) and bulking substances (*e.g.*, lactose, mannitol). The material may be incorporated into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hylauronic acid may also be used. Such compositions may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the present proteins and derivatives. *See, e.g.*, *Martin*, *Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 that are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilised form.

It will be appreciated that pharmaceutical compositions provided according to the present invention may be administered by any means known in the art. Preferably,

the pharmaceutical compositions for administration are administered by injection, orally, or by the pulmonary, or nasal route. The antisense molecules are more preferably delivered by intravenous, intra-arterial, intraperitoneal, intramuscular, or subcutaneous routes of administration.

Antisense molecule based therapy

Also addressed by the present invention is the use of antisense molecules of the present invention, for manufacture of a medicament for modulation of a genetic disease.

The delivery of a therapeutically useful amount of antisense molecules may be achieved by methods previously published. For example, intracellular delivery of the antisense molecule may be via a composition comprising an admixture of the antisense molecule and an effective amount of a block copolymer. An example of this method is described in US patent application US 20040248833.

Other methods of delivery of antisense molecules to the nucleus are described in Mann CJ *et al.*, (2001) ["*Antisense-induced exon skipping and the synthesis of dystrophin in the mdx mouse*". Proc., Natl. Acad. Science, 98(1) 42-47J and in Gebski etal., (2003). Human Molecular Genetics, 12(15): 1801-1811.

A method for introducing a nucleic acid molecule into a cell by way of an expression vector either as naked DNA or complexed to lipid carriers, is described in US patent US 6,806,084.

It may be desirable to deliver the antisense molecule in a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes or liposome formulations.

Liposomes are artificial membrane vesicles which are useful as delivery vehicles *in vitro* and *in vivo*. These formulations may have net cationic, anionic or neutral charge characteristics and are useful characteristics with *in vitro*, *in vivo* and *ex vivo* delivery methods. It has been shown that large unilamellar vesicles (LUV), which range in

size from 0.2-4.0 .PHI.m can encapsulate a substantial percentage of an aqueous buffer containing large macromolecules. RNA, and DNA can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, *et al*., Trends Biochem. Sci., 6:77, 1981).

In order for a liposome to be an efficient gene transfer vehicle, the following characteristics should be present: (1) encapsulation of the antisense molecule of interest at high efficiency while not compromising their biological activity; (2) preferential and substantial binding to a target cell in comparison to non-target cells; (3) delivery of the aqueous contents of the vesicle to the target cell cytoplasm at high efficiency; and (4) accurate and effective expression of genetic information (Mannino, *et al*., Biotechniques, 6:682, 1988).

The composition of the liposome is usually a combination of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations.

Alternatively, the antisense construct may be combined with other pharmaceutically acceptable carriers or diluents to produce a pharmaceutical composition. Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition may be formulated for parenteral, intramuscular, intravenous, subcutaneous, intraocular, oral or transdermal administration.

The routes of administration described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and any dosage for any particular animal and condition. Multiple approaches for introducing functional new genetic material into cells, both *in vitro* and *in vivo* have been attempted (Friedmann (1989) Science, 244:1275-1280).

These approaches include integration of the gene to be expressed into modified retroviruses (Friedmann (1989) supra; Rosenberg (1991) Cancer Research 51(18), suppl.: 5074S-5079S); integration into non-retrovirus vectors (Rosenfeld, *et al*. (1992) Cell,

68:143-155; Rosenfeld, *et al*. (1991) Science, 252:431-434); or delivery of a transgene linked to a heterologous promoter-enhancer element via liposomes (Friedmann (1989), supra; Brigham, *et al*. (1989) Am. J. Med. Sci., 298:278-281; Nabel, *et al*. (1990) Science, 249:1285-1288; Hazinski, *et al*. (1991) Am. J. Resp. Cell Molec. Biol., 4:206-209; and Wang and Huang (1987) Proc. Natl. Acad. Sci. (USA), 84:7851-7855); coupled to ligand-specific, cation-based transport systems (Wu and Wu (1988) J. Biol. Chem., 263:14621-14624) or the use of naked DNA, expression vectors (Nabel et al. (1990), supra); Wolff *et al*. (1990) Science, 247:1465-1468). Direct injection of transgenes into tissue produces only localized expression (Rosenfeld (1992) supra); Rosenfeld *et al*. (1991) supra; Brigham *et al*. (1989) supra; Nabel (1990) supra; and Hazinski *et al*. (1991) supra). The Brigham *et al*. group (Am. J. Med. Sci. (1989) 298:278-281 and Clinical Research (1991) 39 (abstract)) have reported *in vivo* transfection only of lungs of mice following either intravenous or intratracheal administration of a DNA liposome complex. An example of a review article of human gene therapy procedures is: Anderson, Science (1992) 256:808-813.

The antisense molecules of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the compounds of the invention, pharmaceutically acceptable salts of such pro-drugs, and other bioequivalents.

The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: *i.e.*, salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

For oligonucleotides, preferred examples of pharmaceutically acceptable salts include but are not limited to (a) salts formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b)

acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, malefic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polygiutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine. The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including rectal delivery), pulmonary, *e.g.*, by inhalation or insufflation of powders or aerosols, (including by nebulizer, intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intra-arterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Oligonucleotides with at least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration.

The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

<u>Kits of the Invention</u>

The invention also provides kits for treatment of a patient with a genetic disease which kit comprises at least an antisense molecule, packaged in a suitable container, together with instructions for its use.

In a preferred embodiment, the kits will contain at least one antisense molecule as shown in Table 1A, or a cocktail of antisense molecules as shown in Table 1B or a "weasel" compound as shown in Table 1C. The kits may also contain peripheral reagents such as buffers, stabilizers, etc.

Those of ordinary skill in the field should appreciate that applications of the above method has wide application for identifying antisense molecules suitable for use in the treatment of many other diseases.

EXAMPLES

The following Examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these Examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. The references cited herein are expressly incorporated by reference.

Methods of molecular cloning, immunology and protein chemistry, which are not explicitly described in the following examples, are reported in the literature and are known by those skilled in the art. General texts that described conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art, included, for example: Sambrook *et al*, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (1989); Glover ed., *DNA Cloning: A Practical Approach*, Volumes I and II, MRL Press, Ltd., Oxford, U.K. (1985); and Ausubel, F., Brent, R., Kingston, R.E., Moore, D.D., Seidman, J.G., Smith, J.A., Struhl, K. *Current Protocols in Molecular Biology*. Greene Publishing Associates/Wiley Intersciences, New York (2002).

DETERMINING INDUCED EXON SKIPPING IN HUMAN MUSCLE CELLS

Attempts by the inventors to develop a rational approach in antisense molecules design were not completely successful as there did not appear to be a consistent trend that could be applied to all exons. As such, the identification of the most effective

and therefore most therapeutic antisense molecules compounds has been the result of empirical studies.

These empirical studies involved the use of computer programs to identify motifs potentially involved in the splicing process. Other computer programs were also used to identify regions of the pre-mRNA which may not have had extensive secondary structure and therefore potential sites for annealing of antisense molecules. Neither of these approaches proved completely reliable in designing antisense oligonucleotides for reliable and efficient induction of exon skipping.

Annealing sites on the human dystrophin pre-mRNA were selected for examination, initially based upon known or predicted motifs or regions involved in splicing. 2OMe antisense oligonucleotides were designed to be complementary to the target sequences under investigation and were synthesised on an Expedite 8909 Nucleic Acid Synthesiser. Upon completion of synthesis, the oligonucleotides were cleaved from the support column and de-protected in ammonium hydroxide before being desalted. The quality of the oligonucleotide synthesis was monitored by the intensity of the trityl signals upon each deprotection step during the synthesis as detected in the synthesis log. The concentration of the antisense oligonucleotide was estimated by measuring the absorbance of a diluted aliquot at 260nm.

Specified amounts of the antisense molecules were then tested for their ability to induce exon skipping in an *in vitro* assay, as described below.

Briefly, normal primary myoblast cultures were prepared from human muscle biopsies obtained after informed consent. The cells were propagated and allowed to differentiate into myotubes using standard culturing techniques. The cells were then transfected with the antisense oligonucleotides by delivery of the oligonucleotides to the dells as cationic lipoplexes, mixtures of antisense molecules or cationic liposome preparations.

The cells were then allowed to grow for another 24 hours, after which total RNA was extracted and molecular analysis commenced. Reverse transcriptase

amplification (RT-PCR) was undertaken to study the targeted regions of the dystrophin pre-mRNA or induced exonic re-arrangements.

For example, in the testing of an antisense molecule for inducing exon 19 skipping the RT-PCR test scanned several exons to detect involvement of any adjacent exons. For example, when inducing skipping of exon 19, RT-PCR was carried out with primers that amplified across exons 17 and 21. Amplifications of even larger products in this area (*i.e.* exons 13-26) were also carried out to ensure that there was minimal amplification bias for the shorter induced skipped transcript. Shorter or exon skipped products tend to be amplified more efficiently and may bias the estimated of the normal and induced transcript.

The sizes of the amplification reaction products were estimated on an agarose gel and compared against appropriate size standards. The final confirmation of identity of these products was carried out by direct DNA sequencing to establish that the correct or expected exon junctions have been maintained.

Once efficient exon skipping had been induced with one antisense molecule, subsequent overlapping antisense molecules may be synthesized and then evaluated in the assay as described above. Our definition of an efficient antisense molecule is one that induces strong and sustained exon skipping at transfection concentrations in the order of 300 nM or less.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 8

Antisense oligonucleotides directed at exon 8 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 3 shows differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. H8A(-06+18) [SEQ ID NO:1], which anneals to the last 6 bases of intron 7 and the first 18 bases of exon 8, induces substantial exon 8 and 9 skipping when delivered into cells at a concentration of 20 nM. The shorter antisense molecule, H8A(-06+14) [SEQ ID NO: 4] was only able to induce exon 8 and 9 skipping at 300 nM, a

concentration some 15 fold higher than H8A(-06+18), which is the preferred antisense molecule.

This data shows that some particular antisense molecules induce efficient exon skipping while another antisense molecule, which targets a near-by or overlapping region, can be much less efficient. Titration studies show one compound is able to induce targeted exon skipping at 20 nM while the less efficient antisense molecules only induced exon skipping at concentrations of 300 nM and above. Therefore, we have shown that targeting of the antisense molecules to motifs involved in the splicing process plays a crucial role in the overall efficacy of that compound.

Efficacy refers to the ability to induce consistent skipping of a target exon. However, sometimes skipping of the target exons is consistently associated with a flanking exon. That is, we have found that the splicing of some exons is tightly linked. For example, in targeting exon 23 in the mouse model of muscular dystrophy with antisense molecules directed at the donor site of that exon, dystrophin transcripts missing exons 22 and 23 are frequently detected. As another example, when using an antisense molecule directed to exon 8 of the human dystrophin gene, all induced transcripts are missing both exons 8 and 9. Dystrophin transcripts missing only exon 8 are not observed.

Table 2 below discloses antisense molecule sequences that induce exon 8 (and 9) skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
1	H8A(-06+18)	5'-GAU AGG UGG UAU CAA CAU CUG UAA	Very strong to 20 nM
2	H8A (-03+18)	5'-GAU AGG UGG UAU CAA CAU CUG	Very strong skipping to 40nM
3	H8A(-07+18)	5'-GAU AGG UGG UAU CAA CAU CUG UAA G	Strong skipping to 40nM
4	H8A(-06+14)	5'-GGU GGU AUC AAC AUC UGU AA	Skipping to 300nM
5	H8A(-10+10)	5'-GUA UCA ACA UCU GUA AGC AC	Patchy/weak skipping to 100nm

Table 2

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 7

Antisense oligonucleotides directed at exon 7 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 4 shows the preferred antisense molecule, H7A(+45+67) [SEQ ID NO: 6], and another antisense molecule, H7A(+2+26) [SEQ ID NO: 7], inducing exon 7 skipping. Nested amplification products span exons 3 to 9. Additional products above the induced transcript missing exon 7 arise from amplification from carry-over outer primers from the RT-PCR as well as heteroduplex formation.

Table 3 below discloses antisense molecule sequences for induced exon 7 skipping.

SEQ ID	Antisense Oligonucleotid e name	Sequence	Ability to induce skipping
6	H7A(+45+67)	5' - UGC AUG UUC CAG UCG UUG UGU GG	Strong skipping to 20nM
7	H7A(+02+26)	5' - CAC UAU UCC AGU CAA AUA GGU CUG G	Weak skipping at 100nM
8	H7D(+15-10)	5' -AUU UAC CAA CCU UCA GGA UCG AGU A	Weak skipping to 300nM
9	H7A(-18+03)	5' - GGC CUA AAA CAC AUA CAC AUA	Weak skipping to 300nM

Table 3

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 6

Antisense oligonucleotides directed at exon 6 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 5 shows an example of two non-preferred antisense molecules inducing very low levels of exon 6 skipping in cultured human cells. Targeting this exon for specific removal was first undertaken during a study of the canine model using the oligonucleotides as listed in Table 4, below. Some of the human specific oligonucleotides

were also evaluated, as shown in Figure 5. In this example, both antisense molecules target the donor splice site and only induced low levels of exon 6 skipping. Both H6D(+4-21) [SEQ ID NO: 17] and H6D(+18-4) [SEQ ID NO: 18] would be regarded as non-preferred antisense molecules.

One antisense oligonucleotide that induced very efficient exon 6 skipping in the canine model, C6A(+69+91) [SEQ ID NO: 14], would anneal perfectly to the corresponding region in human dystrophin exon 6. This compound was evaluated, found to be highly efficient at inducing skipping of that target exon, as shown in Figure 6 and is regarded as the preferred compound for induced exon 6 skipping. Table 4 below discloses antisense molecule sequences for induced exon 6 skipping.

SEQ ID	Antisense Oligo name	Sequence	Ability to induce skipping
10	C6A(-10+10)	5' CAU UUU UGA CCU ACA UGU GG	No skipping
11	C6A(-14+06)	5' UUU GAC CUA CAU GUG GAA AG	No skipping
12	C6A(-14+12)	5' UAC AUU UUU GAC CUA CAU GUG GAA AG	No skipping
13	C6A(-13+09)	5' AUU UUU GAC CUA CAU GGG AAA G	No skipping
14	CH6A(+69+91)	5' UAC GAG UUG AUU GUC GGA CCC AG	Strong skipping to 20 nM
15	C6D(+12-13)	5' GUG GUC UCC UUA CCU AUG ACU GUG G	Weak skipping at 300 nM
16	C6D(+06-11)	5' GGU CUC CUU ACC UAU GA	No skipping
17	H6D(+04-21)	5' UGU CUC AGU AAU CUU CUU ACC UAU	Weak skipping to 50 nM
18	H6D(+18-04)	5' UCU UAC CUA UGA CUA UGG AUG AGA	Very weak skipping to 300 nM

Table 4

<u>ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 4</u>

Antisense oligonucleotides directed at exon 4 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 7 shows an example of a preferred antisense molecule inducing skipping of exon 4 skipping in cultured human cells. In this example, one preferred antisense compound, H4A(+13+32) [SEQ ID NO:19], which targeted a presumed exonic splicing enhancer induced efficient exon skipping at a concentration of 20 nM while other non-preferred antisense oligonucleotides failed to induce even low levels of exon 4 skipping. Another preferred antisense molecule inducing skipping of exon 4 was H4A(+111+40) [SEQ ID NO:22], which induced efficient exon skipping at a concentration of 20 nM.

Table 5 below discloses antisense molecule sequences for inducing exon 4 skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
19	H4A(+13+32)	5' GCA UGA ACU CUU GUG GAU CC	Skipping to 20 nM
22	H4A(+11+40)	5' UGU UCA GGG CAU GAA CUC UUG UGG AUC CUU	Skipping to 20 nM
20	H4D(+04-16)	5' CCA GGG UAC UAC UUA CAU UA	No skipping
21	H4D(-24-44)	5' AUC GUG UGU CAC AGC AUC CAG	No skipping

Table 5

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 3

Antisense oligonucleotides directed at exon 3 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H3A(+30+60) [SEQ ID NO:23] induced substantial exon 3 skipping when delivered into cells at a concentration of 20 nM to 600 nM. The antisense molecule, H3A(+35+65) [SEQ ID NO: 24] induced exon skipping at 300 nM.

Table 6 below discloses antisense molecule sequences that induce exon 3 skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
23	H3A(+30+60)	UAG GAG GCG CCU CCC AUC CUG UAG GUC ACU G	Moderate skipping to 20 to 600 nM
24	H3A(+35+65)	AGG UCU AGG AGG CGC CUC CCA UCC UGU AGG U	Working to 300 nM
25	H3A(+30+54)	GCG CCU CCC AUC CUG UAG GUC ACU G	Moderate 100-600 nM
26	H3D(+46-21)	CUU CGA GGA GGU CUA GGA GGC GCC UC	No skipping
27	H3A(+30+50)	CUC CCA UCC UGU AGG UCA CUG	Moderate 20-600 nM
28	H3D(+19-03)	UAC CAG UUU UUG CCC UGU CAG G	No skipping
29	H3A(-06+20)	UCA AUA UGC UGC UUCCCA AAC UGA AA	No skipping
30	H3A(+37+61)	CUA GGA GGC GCC UCC CAU CCU GUA G	No skipping

Table 6

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 5

Antisense oligonucleotides directed at exon 5 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H5A(+20+50) [SEQ ID NO:31] induces substantial exon 5 skipping when delivered into cells at a concentration of 100 nM. Table 7 below shows other antisense molecules tested. The majority of these antisense molecules were not as effective at exon skipping as H5A(+20+50). However, H5A(+15+45) [SEQ ID NO: 40] was able to induce exon 5 skipping at 300 nM.

Table 7 below discloses antisense molecule sequences that induce exon 5 skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
31	H5A(+20+50)	UUA UGA UUU CCA UCU ACG AUG UCA GUA CUU C	Working to 100 nM
32	H5D(+25-05)	CUU ACC UGC CAG UGG AGG	No skipping

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
		AUU AUA UUC CAA A	
33	H5D(+10-15)	CAU CAG GAU UCU UAC CUG CCA GUG G	Inconsistent at 300 nM
34	H5A(+10+34)	CGA UGU CAG UAC UUC CAA UAU UCA C	Very weak
35	H5D(-04-21)	ACC AUU CAU CAG GAU UCU	No skipping
36	H5D(+16-02)	ACC UGC CAG UGG AGG AUU	No skipping
37	H5A(-07+20)	CCA AUA UUC ACU AAA UCA ACC UGU UAA	No skipping
38	H5D(+18-12)	CAG GAU UCU UAC CUG CCA GUG GAG GAU UAU	No skipping
39	H5A(+05+35)	ACG AUG UCA GUA CUU CCA AUA UUC ACU AAA U	No skipping
40	H5A(+15+45)	AUU UCC AUC UAC GAU GUC AGU ACU UCC AAU A	Working to 300 nM

Table 7

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 10

Antisense oligonucleotides directed at exon 10 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H10A(-05+16) [SEQ ID NO:41] induced substantial exon 10 skipping when delivered into cells. Table 8 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was variable. Table 8 below discloses antisense molecule sequences that induce exon 10 skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
41	H10A(-05+16)	CAG GAG CUU CCA AAU GCU GCA	Not tested
42	H10A(-05+24)	CUU GUC UUC AGG AGC UUC CAA AUG CUG CA	Not tested
43	H10A(+98+119)	UCC UCA GCA GAA AGA AGC CAC G	Not tested
44	H10A(+130+149)	UUA GAA AUC UCU CCU UGU GC	No skipping
45	H10A(-33-14)	UAA AUU GGG UGU UAC ACA AU	No skipping

Table 8

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 11

Antisense oligonucleotides directed at exon 11 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 8B shows an example of H11A(+75+97) [SEQ ID NO:49] antisense molecule inducing exon 11 skipping in cultured human cells. H11A(+75+97) induced substantial exon 11 skipping when delivered into cells at a concentration of 5 nM. Table 9 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was observed at 100 nM.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
46	H11D(+26+49)	CCC UGA GGC AUU CCC AUC UUG AAU	Skipping at 100 nM
47	H11D(+11-09)	AGG ACU UAC UUG CUU UGU UU	Skipping at 100 nM
48	H11A(+118+140)	CUU GAA UUU AGG AGA UUC AUC UG	Skipping at 100 nM
49	H11A(+75+97)	CAU CUU CUG AUA AUU UUC CUG UU	Skipping at 100 nM
46	H11D(+26+49)	CCC UGA GGC AUU CCC AUC UUG AAU	Skipping at 5nM

Table 9

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 12

Antisense oligonucleotides directed at exon 12 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H12A(+52+75) [SEQ ID NO:50] induced substantial exon 12 skipping when delivered into cells at a concentration of 5 nM, as shown in Figure 8A. Table 10 below shows other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The antisense molecules ability to induce exon skipping was variable.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
50	H12A(+52+75)	UCU UCU GUU UUU GUU AGC CAG UCA	Skipping at 5 nM
51	H12A(-10+10)	UCU AUG UAA ACU GAA AAU UU	Skipping at 100 nM
52	H12A(+11+30)	UUC UGG AGA UCC AUU AAA AC	No skipping

Table 10

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 13

Antisense oligonucleotides directed at exon 13 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H13A(+77+100) [SEQ ID NO:53] induced substantial exon 13 skipping when delivered into cells at a concentration of 5 nM. Table 11 below includes two other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These other antisense molecules were unable to induce exon skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
53	H13A(+77+100)	CAG CAG UUG CGU GAU CUC CAC UAG	Skipping at 5 nM
54	H13A(+55+75)	UUC AUC AAC UAC CAC CAC CAU	No skipping
55	H13D(+06-19)	CUA AGC AAA AUA AUC UGA CCU UAA G	No skipping

Table 11

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 14

Antisense oligonucleotides directed at exon 14 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H14A(+37+64) [SEQ ID NO:56] induced weak exon 14 skipping when delivered into cells at a concentration of 100 nM. Table 12 below includes other antisense

molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
56	H14A(+37+64)	CUU GUA AAA GAA CCC AGC GGU CUU CUG U	Skipping at 100 nM
57	H14A(+14+35)	CAU CUA CAG AUG UUU GCC CAU C	No skipping
58	H14A(+51+73)	GAA GGA UGU CUU GUA AAA GAA CC	No skipping
59	H14D(-02+18)	ACC UGU UCU UCA GUA AGA CG	No skipping
60	H14D(+14-10)	CAU GAC ACA CCU GUU CUU CAG UAA	No skipping
61	H14A(+61 +80)	CAU UUG AGA AGG AUG UCU UG	No skipping
62	H14A(-12+12)	AUC UCC CAA UAC CUG GAG AAG AGA	No skipping

Table 12

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 15

Antisense oligonucleotides directed at exon 15 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H15A(-12+19) [SEQ ID NO:63] and H15A(+48+71) [SEQ ID NO:64] induced substantial exon 15 skipping when delivered into cells at a concentration of 10 Nm, as shown in Figure 9A. Table 13 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 Nm. These other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
63	H15A(-12+19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA CAU U	Skipping at 5Nm
64	H15A(+48+71)	UCU UUA AAG CCA GUU GUG UGA AUC	Skipping at 5Nm
65	H15A(+08+28)	UUU CUG AAA GCC AUG CAC UAA	No skipping
63	H15A(-12+19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA CAU U	No skipping
66	H15D(+17-08)	GUA CAU ACG GCC AGU UUU UGA AGA C	No skipping

Table 13

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 16

Antisense oligonucleotides directed at exon 16 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H16A(-12+19) [SEQ ID NO:67] and H16A(-06+25) [SEQ ID NO:68] induced substantial exon 16 skipping when delivered into cells at a concentration of 10 nM, as shown in Figure 9B. Table 14 below includes other antisense molecules tested. H16A(-06+19) [SEQ ID NO:69] and H16A(+87+109) [SEQ ID NO:70] were tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These two antisense molecules were able to induce exon skipping at 25 nM and 100 nM, respectively. Additional antisense molecules were tested at 100, 200 and 300 nM and did not result in any exon skipping.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
67	H16A(-12+19)	CUA GAU CCG CUU UUA AAA CCU GUU AAA ACA A	Skipping at 5 nM
68	H16A(-06+25)	UCU UUU CUA GAU CCG CUU UUA AAA CCU GUU A	Skipping at 5 nM
69	H16A(-06+19)	CUA GAU CCG CUU UUA AAA CCU GUU A	Skipping at 25 nM
70	H16A(+87+109)	CCG UCU UCU GGG UCA CUG ACU UA	Skipping at 100 nM

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
71	H16A(-07+19)	CUA GAU CCG CUU UUA AAA CCU GUU AA	No skipping
72	H16A(-07+13)	CCG CUU UUA AAA CCU GUU AA	No skipping
73	H16A(+12+37)	UGG AUU GCU UUU UCU UUU CUA GAU CC	No skipping
74	H16A(+92+116)	CAU GCU UCC GUC UUC UGG GUC ACU G	No skipping
75	H16A(+45+67)	G AUC UUG UUU GAG UGA AUA CAG U	No skipping
76	H16A(+105+126)	GUU AUC CAG CCA UGC UUC CGU C	No skipping
77	H16D(+05-20)	UGA UAA UUG GUA UCA CUA ACC UGU G	No skipping
78	H16D(+12-11)	GUA UCA CUA ACC UGU GCU GUA C	No skipping

Table 14

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 19

Antisense oligonucleotides directed at exon 19 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H19A(+35+65) [SEQ ID NO:79] induced substantial exon 19 skipping when delivered into cells at a concentration of 10 nM. This antisense molecule also showed very strong exon skipping at concentrations of 25, 50, 100, 300 and 600 nM.

Figure 10 illustrates exon 19 and 20 skipping using a "cocktail" of antisense oligonucleotides, as tested using gel electrophoresis. It is interesting to note that it was not easy to induce exon 20 skipping using single antisense oligonucleotides H20A(+44+71) [SEQ ID NO:81] or H20A(+149+170) [SEQ ID NO:82], as illustrated in sections 2 and 3 of the gel shown in Figure 10. Whereas, a "cocktail" of antisense oligonucleotides was more efficient as can be seen in section 4 of Figure 10 using a "cocktail" of antisense oligonucleotides H20A(+44+71) and H20A(+149+170). When the cocktail was used to target exon 19, skipping was even stronger (see section 5, Figure 10).

Figure 11 illustrates gel electrophoresis results of exon 19/20 skipping using "weasels" The "weasels" were effective in skipping exons 19 and 20 at concentrations of 25, 50, 100, 300 and 600 nM. A further "weasel" sequence is shown in the last row of Table 3C. This compound should give good results.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 20

Antisense oligonucleotides directed at exon 20 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

None of the antisense oligonucleotides tested induced exon 20 skipping when delivered into cells at a concentration of 10, 25, 50, 300 or 600 nM (see Table 15). Antisense molecules H20A(-11+17) [SEQ ID NO:86] and H20D(+08-20) [SEQ ID NO:87] are yet to be tested.

However, a combination or "cocktail" of H20A(+44+71) [SEQ ID NO: 81] and H20(+149+170) [SEQ ID NO:82] in a ratio of 1:1, exhibited very strong exon skipping at a concentration of 100 nM and 600 nM. Further, a combination of antisense molecules H19A(+35+65) [SEQ ID NO:79], H20A(+44+71) [SEQ ID NO:81] and H20A(+149+170) [SEQ ID NO:82] in a ratio of 2:1:1, induced very strong exon skipping at a concentration ranging from 10 nM to 600 nM.

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
81	H20A(+44+71)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C	No skipping
82	H20A(+147+168)	CAG CAG UAG UUG UCA UCU GCU C	No skipping
83	H20A(+185+203)	UGA UGG GGU GGU GGG UUG G	No skipping
84	H20A(-08+17)	AUC UGC AUU AAC ACC CUC UAG AAA G	No skipping
85	H20A(+30+53)	CCG GCU GUU CAG UUG UUC UGA GGC	No skipping
86	H20A(-11+17)	AUC UGC AUU AAC ACC CUC UAG AAA GAA A	Not tested yet
87	H20D(+08-20)	GAA GGA GAA GAG AUU CUU ACC UUA CAA A	Not tested yet
81 & 82	H20A(+44+71) & H20A(+147+168)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C CAG CAG UAG UUG UCA UCU GCU C	Very strong skipping
80, 81	H19A(+35+65);	GCC UGA GCU GAU CUG CUG GCA UCU	Very strong

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
& 82	H20A(+44+71); H20A(+147+168)	UGC AGU U; CUG GCA GAA UUC GAU CCA CCG GCU GUU C; CAG CAG UAG UUG UCA UCU GCU C	skipping

Table 15

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 21

Antisense oligonucleotides directed at exon 21 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H21A(+85+108) [SEQ ID NO:92] and H21A(+85+106) [SEQ ID NO:91] induced exon 21 skipping when delivered into cells at a concentration of 50 nM. Table 16 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
90	H21A(-06+16)	GCC GGU UGA CUU CAU CCU GUG C	Skips at 600 nM
91	H21A(+85+106)	CUG CAU CCA GGA ACA UGG GUC C	Skips at 50 nM
92	H21A(+85+108)	GUC UGC AUC CAG GAA CAU GGG UC	Skips at 50 nM
93	H21A(+08+31)	GUU GAA GAU CUG AUA GCC GGU UGA	Skips faintly to
94	H21D(+18-07)	UAC UUA CUG UCU GUA GCU CUU UCU	No skipping

Table 16

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 22

Antisense oligonucleotides directed at exon 22 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 12 illustrates differing efficiencies of two antisense molecules directed at exon 22 acceptor splice site. H22A(+125+106) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO: 98] induce strong exon 22 skipping from 50 nM to 600 nM concentration.

H22A(+125+146) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO:98] induced exon 22 skipping when delivered into cells at a concentration of 50 nM. Table 17 below shows other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed a variable ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
95	H22A(+22+45)	CAC UCA UGG UCU CCU GAU AGC GCA	No skipping
96	H22A(+125+146)	CUG CAA UUC CCC GAG UCU CUG C	Skipping to 50 nM
97	H22A(+47+69)	ACU GCU GGA CCC AUG UCC UGA UG	Skipping to 300 nM
98	H22A(+80+101)	CUA AGU UGA GGU AUG GAG AGU	Skipping to 50 nM
99	H22D(+13-11)	UAU UCA CAG ACC UGC AAU UCC CC	No skipping

Table 17

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 23

Antisense oligonucleotides directed at exon 23 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 18 below shows antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed no ability to induce exon skipping or are yet to be tested.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
100	H23A(+34+59)	ACA GUG GUG CUG AGA UAG UAU AGG CC	No skipping
101	H23A(+18+39)	UAG GCC ACU UUG UUG CUC UUG C	No Skipping
102	H23A(+72+90)	UUC AGA GGG CGC UUU CUU C	No Skipping

Table 18

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 24

Antisense oligonucleotides directed at exon 24 were prepared using similar methods as described above. Table 19 below outlines the antisense oligonucleotides directed at exon 24 that are yet to be tested for their ability to induce exon 24 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
103	H24A(+48+70)	GGG CAG GCC AUU CCU CCU UCA GA	Needs testing
104	H24A(-02+22)	UCU UCA GGG UUU GUA UGU GAU UCU	Needs testing

Table 19

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 25

Antisense oligonucleotides directed at exon 25 were prepared using similar methods as described above. Table 20 below shows the antisense oligonucleotides directed at exon 25 that are yet to be tested for their ability to induce exon 25 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
105	H25A(+9+36)	CUG GGC UGA AUU GUC UGA AUA UCA CUG	Needs testing
106	H25A(+131+156)	CUG UUG GCA CAU GUG AUC CCA CUG AG	Needs testing
107	H25D(+16-08)	GUC UAU ACC UGU UGG CAC AUG UGA	Needs testing

Table 20

ANTISENSE OLIGONUCIEOTIDES DIRECTED AT EXON 26

Antisense oligonucleotides directed at exon 26 were prepared using similar methods as described above. Table 21 below outlines the antisense oligonucleotides directed at exon 26 that are yet to be tested for their ability to induce exon 26 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
108	H26A(+132+156)	UGC UUU CUG UAA UUC AUC UGG AGU U	Needs testing
109	H26A(-07+19)	CCU CCU UUC UGG CAU AGA CCU UCC AC	Needs testing
110	H26A(+68+92)	UGU GUC AUC CAU UCG UGC AUC UCU G	Faint skipping at 600 nM

Table 21

ANTISENSE OLIQONUCLEOTIDES DIRECTED AT EXON 27

Antisense oligonucleotides directed at exon 27 were prepared using similar methods as described above. Table 22 below outlines the antisense oligonucleotides directed at exon 27 that are yet to be tested for their ability to induce exon 27 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
111	H27A(+82+106)	UUA AGG CCU CUU GUG CUA CAG GUG G	Needs testing
112	H27A(-4+19)	GGG CCU CUU CUU UAG CUC UCU GA	Faint skipping at 600 and 300 nM
113	H27D(+19-03)	GAC UUC CAA AGU CUU GCA UUU C	v. strong skipping at 600 and 300 nM

Table 22

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 28

Antisense oligonucleotides directed at exon 28 were prepared using similar methods as described above. Table 23 below outlines the antisense oligonucleotides directed at exon 28 that are yet to be tested for their ability to induce exon 28 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
114	H28A(-05+19)	GCC AAC AUG CCC AAA CUU CCU AAG	v. strong skipping at 600 and 300 nM
115	H28A(+99+124)	CAG AGA UUU CCU CAG CUC CGC CAG GA	Needs testing
116	H28D(+16-05)	CUU ACA UCU AGC ACC UCA GAG	v. strong skipping at 600 and 300 nM

Table 23

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 29

Antisense oligonucleotides directed at exon 29 were prepared using similar methods as described above. Table 24 below outlines the antisense oligonucleotides directed at exon 29 that are yet to be tested for their ability to induce exon 29 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
117	H29A(+57+81)	UCC GCC AUC UGU UAG GGU CUG UGC C	Needs testing
118	H29A(+18+42)	AUU UGG GUU AUC CUC UGA AUG UCG C	v. strong skipping at 600 and 300 nM
119	H29D(+17-05)	CAU ACC UCU UCA UGU AGU UCC C	v. strong skipping at 600 and 300 nM

Table 24

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 30

Antisense oligonucleotides directed at exon 30 were prepared using similar methods as described above. Table 25 below outlines the antisense oligonucleotides directed at exon 30 that are yet to be tested for their ability to induce exon 30 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
120	H30A(+122+147)	CAU UUG AGC UGC GUC CAC CUU GUC UG	Needs testing
121	H30A(+25+50)	UCC UGG GCA GAC UGG AUG CUC UGU UC	Very strong skipping at 600 and 300 nM.
122	H30D(+19-04)	UUG CCU GGG CUU CCU GAG GCA UU	Very strong skipping at 600 and 300 nM.

Table 25

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 31

Antisense oligonucleotides directed at exon 31 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 13 illustrates differing efficiencies of two antisense molecules directed at exon 31 acceptor splice site and a "cocktail" of exon 31 antisense oligonucleotides at varying concentrations. H31D(+03-22) [SEQ ID NO:124] substantially induced exon 31 skipping when delivered into cells at a concentration of 20 nM. Table 26 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
123	H31D(+06-18)	UUC UGA AAU AAC AUA UAC CUG UGC	Skipping to 300 nM
124	H31D(+03-22)	UAG UUU CUG AAA UAA CAU AUA CCU G	Skipping to 20 nM
125	H31A(+05+25)	GAC UUG UCA AAU CAG AUU GGA	No skipping
126	H31D(+04-20)	GUU UCU GAA AUA ACA UAU ACC UGU	Skipping to 300 nM

Table 26

ANTISENSE OLIGONUCTEOTIDES DIRECTED AT EXON 32

Antisense oligonucleotides directed at exon 32 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H32D(+04-16) [SEQ ID NO:127] and H32A(+49+73) [SEQ ID NO:130] induced exon 32 skipping when delivered into cells at a concentration of 300 nM. Table 27 below also shows other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules did not show an ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
127	H32D(+04-16)	CAC CAG AAA UAC AUA CCA CA	Skipping to 300 nM
128	H32A(+151+170)	CAA UGA UUU AGC UGU GAC UG	No skipping
129	H32A(+10+32)	CGA AAC UUC AUG GAG ACA UCU UG	No skipping
130	H32A(+49+73)	CUU GUA GAC GCU GCU CAA AAU UGG C	Skipping to 300 nM

Table 27

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 33

Antisense oligonucleotides directed at exon 33 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 14 shows differing efficiencies of two antisense molecules directed at exon 33 acceptor splice site. H33A(+64+88) [SEQ ID NO:134] substantially induced exon 33 skipping when delivered into cells at a concentration of 10 nM. Table 28 below includes other antisense molecules tested at a concentration of 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
131	H33D(+09-11)	CAU GCA CAC ACC UUU GCU CC	No skipping
132	H33A(+53+76)	UCU GUA CAA UCU GAC GUC CAG UCU	Skipping to 200 nM
133	H33A(+30+56)	GUG UUU AUC ACC AUU UCC ACU UCA GAC	Skipping to 200 nM
134	H33A(+64+88)	GCG UCU GCU UUU UCU GUA CAA UCU G	Skipping to 10 nM

Table 28

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 34

Antisense oligonucleotides directed at exon 34 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 29 below includes antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
135	H34A(+83+104)	UCC AUA UCU GUA GCU GGC AGC C	No skipping
136	H34A(+143+165)	CCA GGC AAC UUC AGA AUC CAA AU	No skipping
137	H34A(-20+10)	UUU CUG UUA CCU GAA AAG AAU UAU AAU GAA	Not tested
138	H34A(+46+70)	CAU UCA UUU CCU UUC GCA UCU UAC G	Skipping to 300 nM
139	H34A(+95+120)	UGA UCU CUU UGU CAA UUC CAU AUC UG	Skipping to 300 nM
140	H34D(+10-20)	UUC AGU GAU AUA GGU UUU ACC UUU CCC CAG	Not tested
141	H34A(+72+96)	CUG UAG CUG CCA GCC AUU CUG UCA AG	No skipping

Table 29

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 35

Antisense oligonucleotides directed at exon 35 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 15 shows differing efficiencies of antisense molecules directed at exon 35 acceptor splice site. H35A(+24+43) [SEQ ID NO:144] substantially induced exon 35 skipping when delivered into cells at a concentration of 20 nM. Table 30 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed no ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
142	H35A(+141+161)	UCU UCU GCU CGG GAG GUG ACA	Skipping to 20 nM
143	H35A(+116+135)	CCA GUU ACU AUU CAG AAG AC	No skipping
144	H35A(+24+43)	UCU UCA GGU GCA CCU UCU GU	No skipping

Table 30

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 36

Antisense oligonucleotides directed at exon 36 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense molecule H36A(+26+50) [SEQ ID NO:145] induced exon 36 skipping when delivered into cells at a concentration of 300 nM, as shown in Figure 16.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 37

Antisense oligonucleotides directed at exon 37 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 17 shows differing efficiencies of two antisense molecules directed at exon 37 acceptor splice site. H37A(+82+105) [SEQ ID NO:148] and H37A(+134+157)

[SEQ ID NO:149] substantially induced exon 37 skipping when delivered into cells at a concentration of 10 nM. Table 31 below shows the antisense molecules tested.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
147	H37A(+26+50)	CGU GUA GAG UCC ACC UUU GGG CGU A	No skipping
148	H37A(+82+105)	UAC UAA UUU CCU GCA GUG GUC ACC	Skipping to 10 nM
149	H37A(+134+157)	UUC UGU GUG AAA UGG CUG CAA AUC	Skipping to 10 nM

Table 31

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 38

Antisense oligonucleotides directed at exon 38 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 18 illustrates antisense molecule H38A(+88+112) [SEQ ID NO:152] , directed at exon 38 acceptor splice site. H38A(+88+112) substantially induced exon 38 skipping when delivered into cells at a concentration of 10 nM. Table 32 below shows the antisense molecules tested and their ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
150	H38A(-01+19)	CCU UCA AAG GAA UGG AGG CC	No skipping
151	H38A(+59+83)	UGC UGA AUU UCA GCC UCC AGU GGU U	Skipping to 10 nM
152	H38A(+88+112)	UGA AGU CUU CCU CUU UCA GAU UCA C	Skipping to 10 nM

Table 32

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 39

Antisense oligonucleotides directed at exon 39 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H39A(+62+85) [SEQ ID NO:153] induced exon 39 skipping when delivered into cells at a concentration of 100 nM. Table 33 below shows the antisense molecules tested and their ability to induce exon skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
153	H39A(+62+85)	CUG GCU UUC UCU CAU CUG UGA UUC	Skipping to 100 nM
154	H39A(+39+58)	GUU GUA AGU UGU CUC CUC UU	No skipping
155	H39A(+102+121)	UUG UCU GUA ACA GCU GCU GU	No skipping
156	H39D(+10-10)	GCU CUA AUA CCU UGA GAG CA	Skipping to 300 nM

Table 33

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 40

Antisense oligonucleotides directed at exon 40 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 19 illustrates antisense molecule H40A(-05+17) [SEQ ID NO:157] directed at exon 40 acceptor splice site. H40A(-05+17) and H40A(+129+153) [SEQ ID NO:158] both substantially induced exon 40 skipping when delivered into cells at a concentration of 5 nM.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 42

Antisense oligonucleotides directed at exon 42 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 20 illustrates antisense molecule H42A(-04+23) [SEQ ID NO:159], directed at exon 42 acceptor splice site. H42A(-4+23) and H42D(+19-02) [SEQ ID NO:161] both induced exon 42 skipping when delivered into cells at a concentration of 5 nM. Table 34 below shows the antisense molecules tested and their ability to induce exon 42 skipping.

SEQ ID	Antisense afigonucleotide name	Sequence	Ability to induce skipping
159	H42A(-4+23)	AUC GUU UCU UCA CGG ACA GUG UGG UGC	Skipping to 5 nM
160	H42A(+86+109)	GGG CUU GUG AGA CAU GAG UGA UUU	Skipping to 100 nM
161	H42D(+19-02)	A CCU UCA GAG GAC UCC UCU UGC	Skipping to 5 nM

Table 34

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 43

Antisense oligonucleotides directed at exon 43 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H43A(+101+120) [SEQ ID NO:163] induced exon 43 skipping when delivered into cells at a concentration of 25 nM. Table 35 below includes the antisense molecules tested and their ability to induce exon 43 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
162	H43D(+10-15)	UAU GUG UUA CCU ACC CUU GUC GGU C	Skipping to 100 nM
163	H43A(+101+120)	GGA GAG AGC UUC CUG UAG CU	Skipping to 25 nM
164	H43A(+78+100)	UCA CCC UUU CCA CAG GCG UUG CA	Skipping to 200 n M

Table 35

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 44

Antisense oligonucleotides directed at exon 44 were prepared using similar methods as described above. Testing fior the ability of these antisense molecules to induce exon 44 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 165 to 167 in Table 1A.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 45

Antisense oligonucleotides directed at exon 45 were prepared using similar methods as described above. Testing for the ability of these antisense molecules to induce exon 45 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 207 to 211 in Table 1A.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 46

Antisense oligonucleotides directed at exon 46 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 21 illustrates the efficiency of one antisense molecule directed at exon 46 acceptor splice site. Antisense oligonucleotide H46A(+86+115) [SEQ ID NO:203] showed very strong ability to induce exon 46 skipping. Table 36 below includes antisense molecules tested. These antisense molecules showed varying ability to induce exon 46 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
168	H46D(+16-04)	UUA CCU UGA CUU GCU CAA GC	No skipping
169	H46A(+90+109)	UCC AGG UUC AAG UGG GAU AC	No skipping
203	H46A(+86+115)	CUC UUU UCC AGG UUC AAG UGG GAU ACU AGC	Good skipping to 100 nM
204	H46A(+107+137)	CAA GCU UUU CUU UUA GUU GCU GCU CUU UUC C	Good skipping to 100 nM
205	H46A(-10+20)	UAU UCU UUU GUU CUU CUA GCC UGG AGA AAG	Weak skipping
206	H46A(+50+77)	CUG CUU CCU CCA ACC AUA AAA CAA AUU C	Weak skipping

Table 36

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 47

Antisense oligonucleotides directed at exon 47 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H47A(+76+100) [SEQ ID NO:170] and H47A(-09+12) [SEQ ID NO:172] both induced exon 47 skipping when delivered into cells at a concentration of 200 nM. H47D(+25-02) [SEQ ID NO: 171] is yet to be prepared and tested.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 50

Antisense oligonucleotides directed at exon 50 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense oligonucleotide molecule H50A(+02+30) [SEQ ID NO: 173] was a strong inducer of exon skipping. Further, H50A(+07+33) [SEQ ID NO:174] and H50D(+07-18) [SEQ ID NO:175] both induced exon 50 skipping when delivered into cells at a concentration of 100 nM.

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 51

Antisense oligonucleotides directed at exon 51 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 22 illustrates differing efficiencies of two antisense molecules directed at exon 51 acceptor splice site. Antisense oligonucleotide H51A(+66+90) [SEQ ID NO:180] showed the stronger ability to induce exon 51 skipping. Table 37 below includes antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 51 skipping. The strongest inducers of exon skipping were antisense oligonucleotide H51A(+61+90) [SEQ ID NO: 179] and H51A(+66+95) [SEQ ID NO: 181].

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
176	H51A(-01+25)	ACC AGA GUA ACA GUC UGA GUA GGA GC	Faint skipping
177	H51D(+16-07)	CUC AUA CCU UCU GCU UGA UGA UC	Skipping at 300 nM
178	H51A(+111+134)	UUC UGU CCA AGC CCG GUU GAA AUC	Needs re- testing
179	H51A(+61+90)	ACA UCA AGG AAG AUG GCA UUU CUA GUU UGG	Very strong skipping
180	H51A(+66+90)	ACA UCA AGG AAG AUG GCA UUU CUA G	skipping
181	H51A(+66+95)	CUC CAA CAU CAA GGA AGA UGG CAU UUC UAG	Very strong skipping
182	H51D(+08-17)	AUC AUU UUU UCU CAU ACC UUC UGC U	No skipping
183	H51A/D(+08-17) & (-15+?)	AUC AUU UUU UCU CAU ACC UUC UGC UAG GAG CUA AAA	No skipping
184	H51A(+175+195)	CAC CCA CCA UCA GCC UCU GUG	No skipping
185	H51A(+199+220)	AUC AUC UCG UUG AUA UCC UCA A	No skipping

Table 37

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 52

Antisense oligonucleotides directed at exon 52 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 22 also shows differing efficiencies of four antisense molecules directed at exon 52 acceptor splice site. The most effective antisense oligonucleotide for inducing exon 52 skipping was H52A(+17+37) [SEQ ID NO:188).

Table 38 below shows antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 50 skipping. Antisense molecules H52A(+12+41) [SEQ ID NO:187] and

H52A(+17+37) [SEQ ID NO:188] showed the strongest exon 50 skipping at a concentration of 50 nM.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
186	H52A(-07+14)	UCC UGC AUU GUU GCC UGU AAG	No skipping
187	H52A(+12+41)	UCC AAC UGG GGA CGC CUC UGU UCC AAA UCC	Very strong skipping
188	H52A(+17+37)	ACU GGG GAC GCC UCU GUU CCA	Skipping to 50 nM
189	H52A(+93+112)	CCG UAA UGA UUG UUC UAG CC	No skipping
190	H52D(+05-15)	UGU UAA AAA ACU UAC UUC GA	No skipping

Table 38

ANTISENSE OLIGONUCLEOTIDES DIRECTED AT EXON 53

Antisense oligonucleotides directed at exon 53 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Figure 22 also shows antisense molecule H53A(+39+69) [SEQ ID NO:193] directed at exon 53 acceptor splice site. This antisense oligonucleotide was able to induce exon 53 skipping at 5, 100, 300 and 600 nM. A "cocktail" of three exon 53 antisense oligonucleotides: H53A(+23+47) [SEQ ID NO:195], H53A(+150+176) [SEQ ID NO:196] and H53D(+14-07) [SEQ ID NO:194], was also tested, as shown in Figure 20 and exhibited an ability to induce exon skipping.

Table 39 below includes other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 53 skipping. Antisense molecule H53A(+39+69) [SEQ ID NO:193] induced the strongest exon 53 skipping.

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
191	H53A(+45+69)	CAU UCA ACU GUU GCC UCC GGU UCU G	Faint skipping at 50 nM
192	H53A(+39+62)	CUG UUG CCU CCG GUU CUG AAG GUG	Faint skipping at 50 nM
193	H53A(+39+69)	CAU UCA ACU GUU GCC UCC GGU UCU GAA GGU G	Strong skipping to 50 nM
194	H53D(+14-07)	UAC UAA CCU UGG UUU CUG UGA	Very faint skipping to 50 nM
195	H53A(+23+47)	CUG AAG GUG UUC UUG UAC UUC AUC C	Very faint skipping to 50 nM
196	H53A(+150+176)	UGU AUA GGG ACC CUC CUU CCA UGA CUC	Very faint skipping to 50 nM
197	H53D(+20-05)	CUA ACC UUG GUU UCU GUG AUU UUC U	Not made yet
198	H53D(+09-18)	GGU AUC UUU GAU ACU AAC CUU GGU UUC	Faint at 600 nM
199	H53A(-12+10)	AUU CUU UCA ACU AGA AUA AAA G	No skipping
200	H53A(-07+18)	GAU UCU GAA UUG UUU CAA CUA GAA U	No skipping
201	H53A(+07+26)	AUC CCA CUG AUU CUG AAU UC	No skipping
202	H53A(+124+145)	UUG GCU CUG GCC UGU CCU AAG A	No skipping

Table 39

The Claims Defining the Invention are as Follows

1. An antisense molecule capable of binding to a selected target site to induce exon skipping in the dystrophin gene, as set forth in SEQ ID NO: 1 to 202.

2. An antisense molecule according to claim 1 capable of inducing exon skipping in exons 3, 4, 8, 10 to 16, 19 to 40, 42 to 44, 46, 47 and 50 to 53 of the dystrophin gene.

3. A combination of two or more antisense molecules according to claim 1 or 2 capable of binding to a selected target to induce exon skipping in the dystrophin gene.

4. A combination or two or more antisense molecules according to claim 3 selected from Table 1B.

5. A combination of two or more antisense molecules according to claim 1 or 2 joined together to form a "weasel", wherein said weasel is capable of binding to a selected target to induce exon skipping in the dystrophin gene.

6. A combination of two or more antisense molecules according to claim 5 selected from Table 1C.

7. The antisense molecule according to any one of claims 1 to 6, capable of binding to a selected target site, wherein the target site is an rnRNA splicing site selected from a splicer donor site, splice acceptor sites or exonic splicing enhancer elements.

8. A method of treating muscular dystrophy in a patient comprising administering to the patient a composition comprising an antisense molecule according to anyone of claims 1 to 6.

9. A pharmaceutical or therapeutic composition for the treatment of muscular dystrophy in a patient comprising (a) at least an antisense molecule according to any one of claims 1 to 6, and (b) one or more pharmaceutically acceptable carriers and/or diluents.

10. The composition according to claim 9, comprising about 20 nM to 600 nM of the antisense molecule.

11. The use of an antisense molecule according to any one of claims 1 to 6 for the manufacture of a medicament for modulation of muscular dystrophy.

12. An antisense molecule according to any one of claims 1 to 6 for use in antisense molecule based therapy.

13. An antisense molecule according to any one of claims 1 to 6 as herein before described with reference to the examples.

14. A kit comprising at least one antisense molecule according to any one of claims 1 to 6, a suitable carrier and instructions for its use.

ABSTRACT

An antisense molecule capable of binding to a selected target site to induce exon skipping in the dystrophin gene, as set forth in SEQ ID NO: 1 to 202.

FIGURE 1

bp Acceptor ESE Donor

uc$\boxed{\text{a}}$ugcacugaguga$\boxed{\text{ccucuuucucgcagG}}$CGCUAGC$\boxed{\text{UGGAG}}$CA/////CCGUGCAGACUGA$\boxed{\text{CGgucuca}}$u

SEQ ID NO:213

SEQ ID NO:214

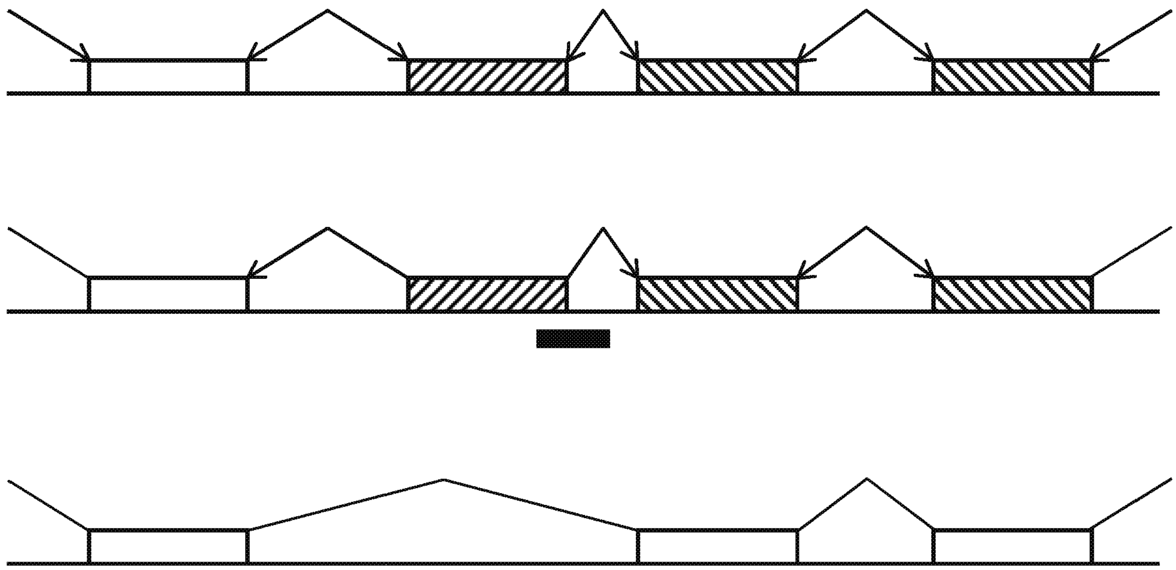


FIGURE 2

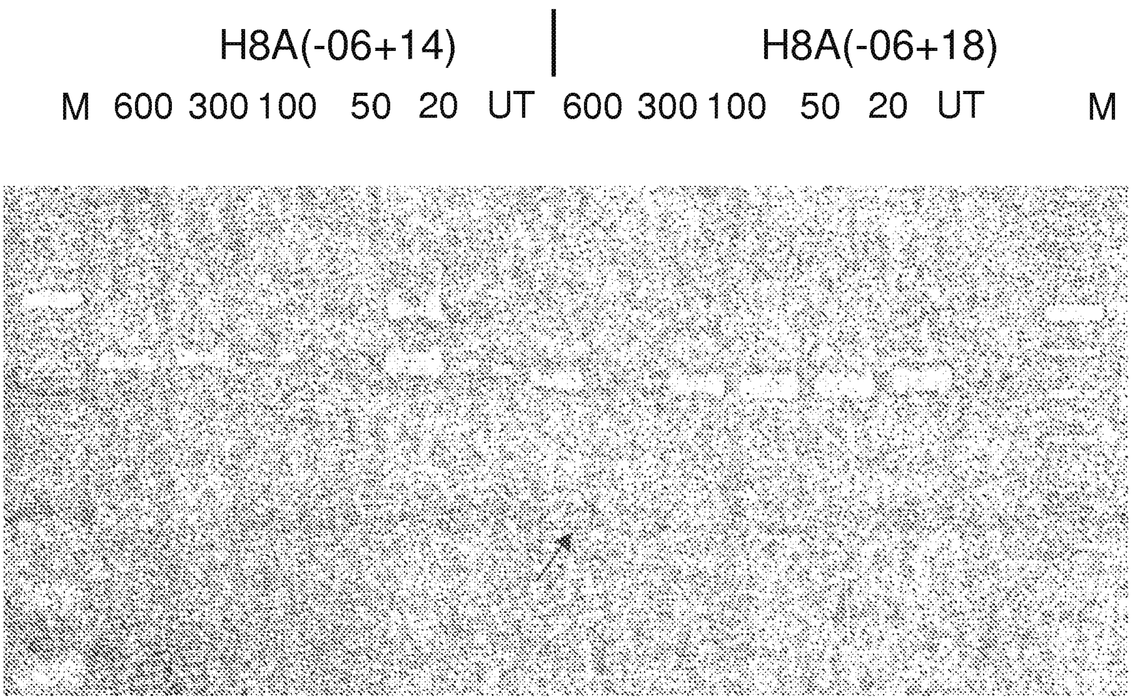


FIGURE 3

H7A(+45+67) H7A(+2+26)

M 600 300 100 50 20 600NM 600 300 100 50 20 600N M

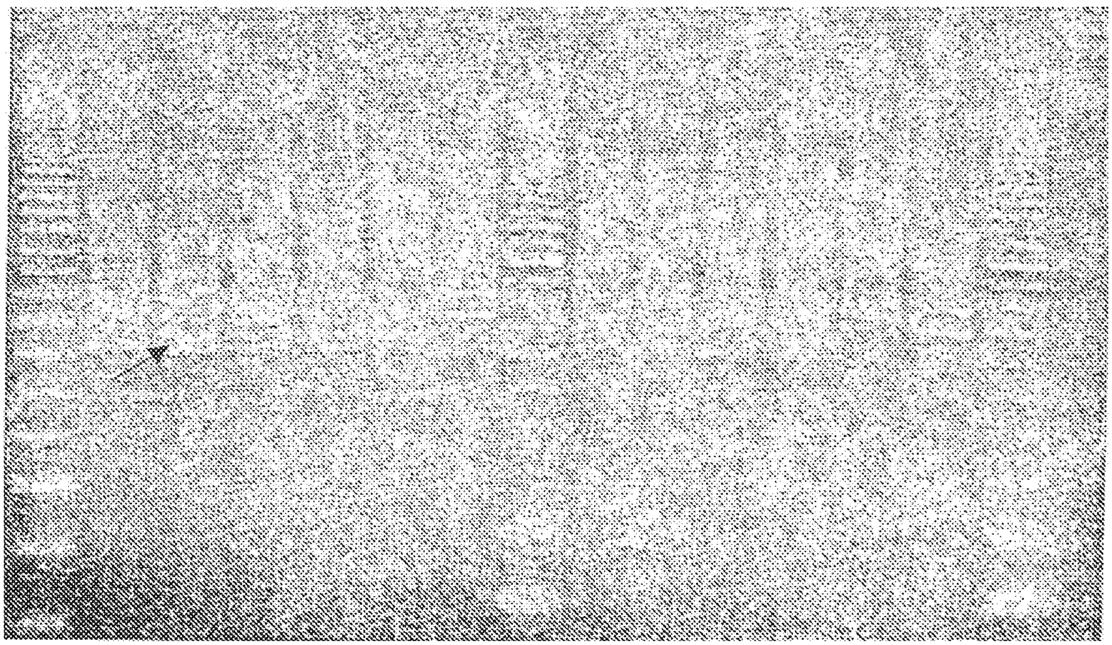


FIGURE 4

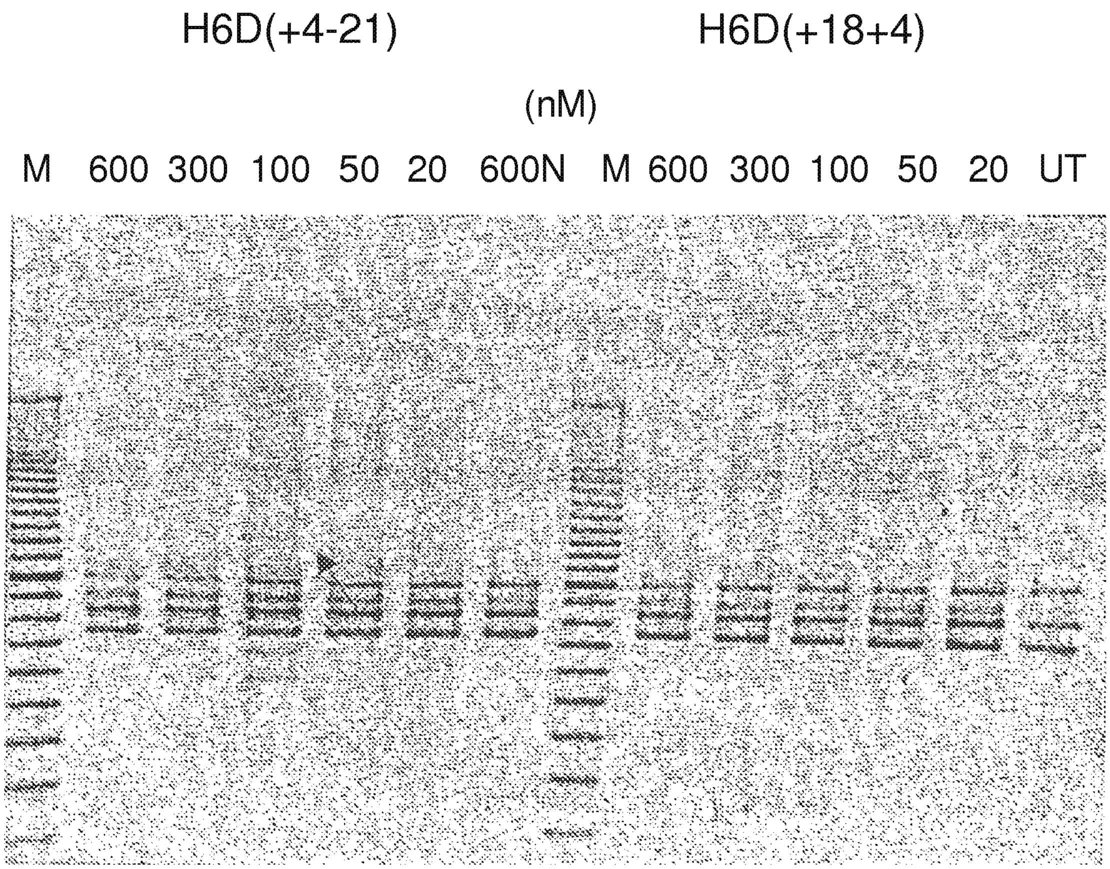


FIGURE 5

6A(+69+91)

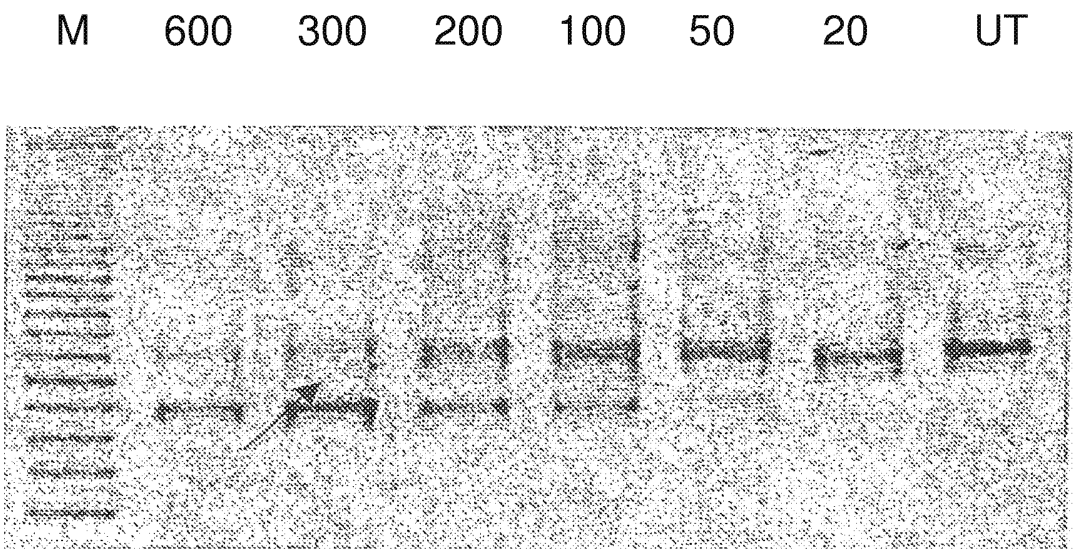


FIGURE 6

H4A(+13+32)

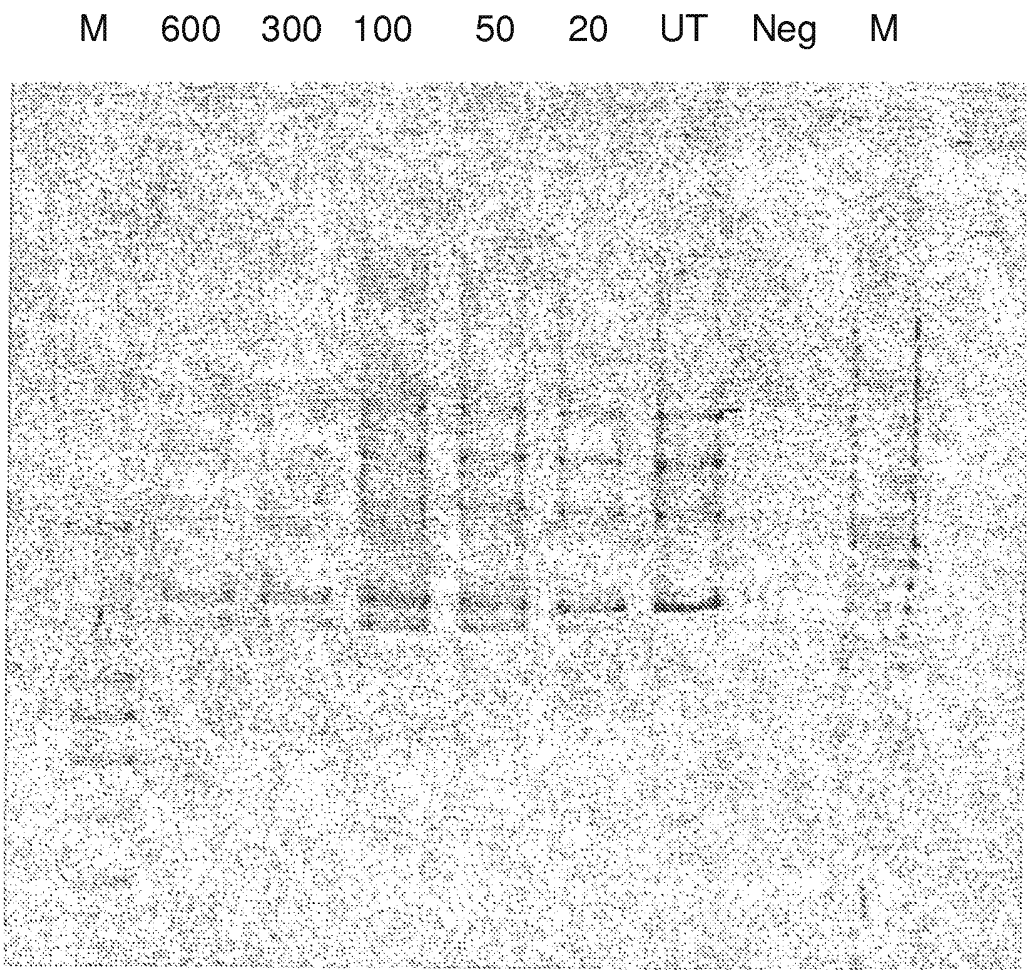
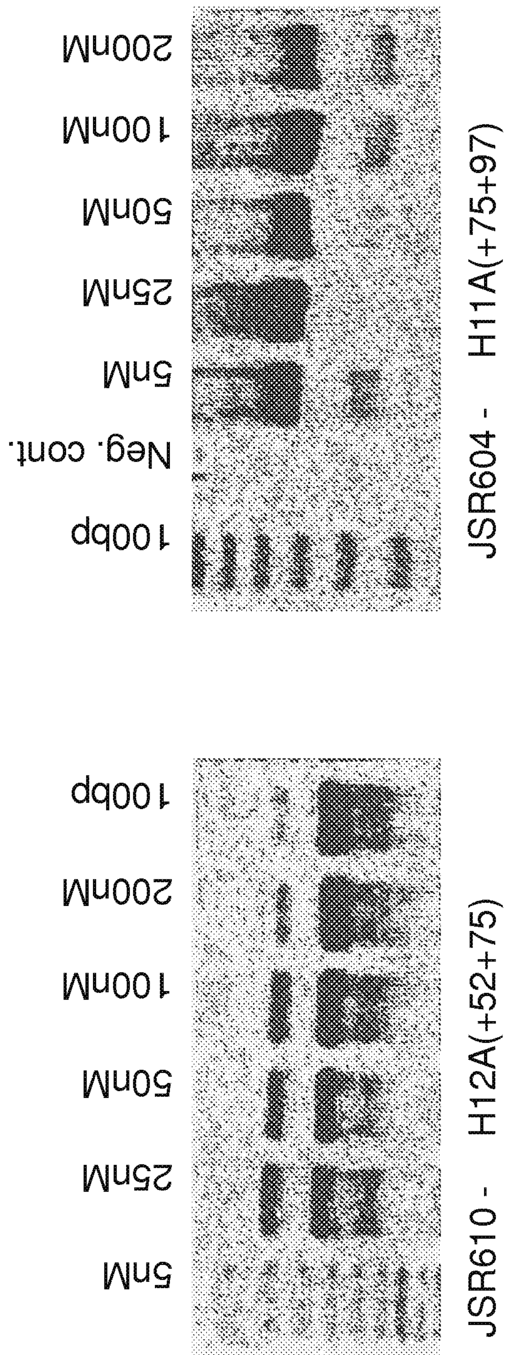


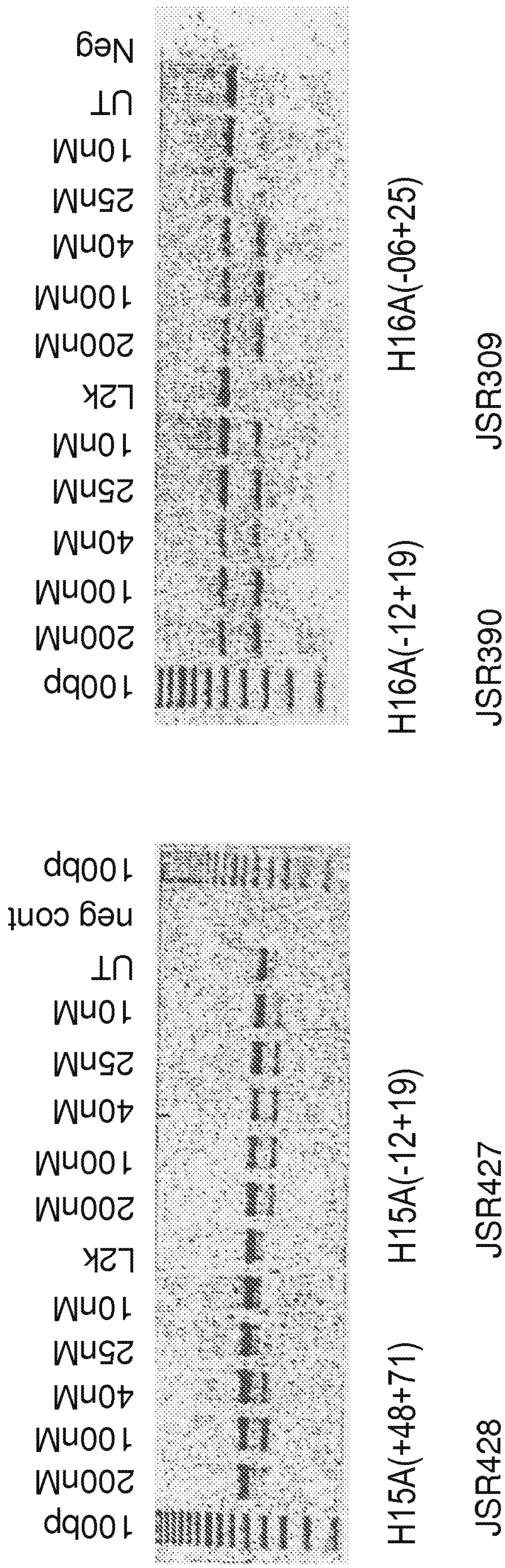
FIGURE 7


5nM
25nM
50nM
100nM
200nM
100bp
JSR610 - H12A(+52+75)
100bp
Neg. cont.
5nM
25nM
50nM
100nM
200nM
JSR604 - H11A(+75+97)

A

B

FIGURE 8


100bp
200nM
100nM
40nM
25nM
10nM
L2K
200nM
100nM
40nM
25nM
10nM
UT
neg cont
100bp
H15A(+48+71)
JSR428
H15A(-12+19)
JSR427
100bp
200nM
100nM
40nM
25nM
10nM
L2K
200nM
100nM
40nM
25nM
10nM
UT
Neg
H16A(-12+19)
JSR390
H16A(-06+25)
JSR309

A

B

FIGURE 9

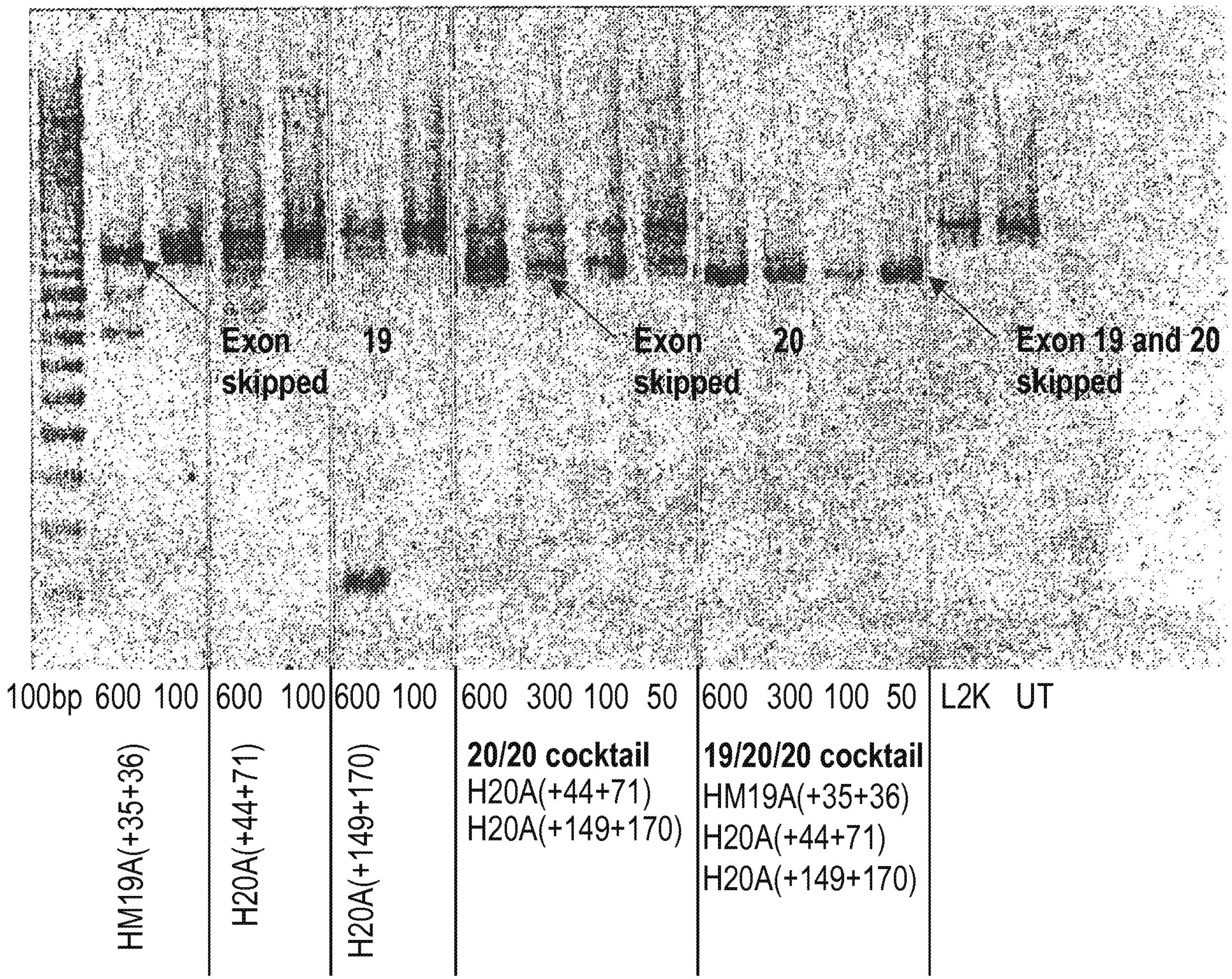
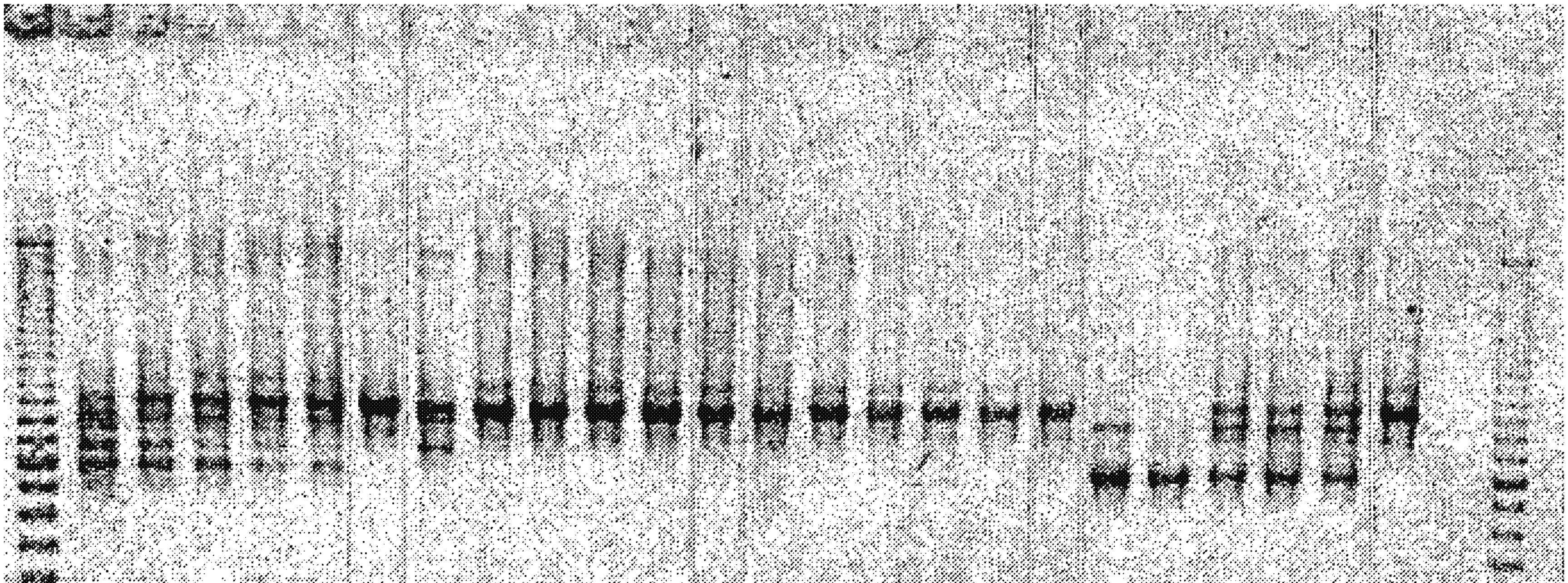

Exon 19 skipped
Exon 20 skipped
Exon 19 and 20 skipped
100bp 600 100 600 100 600 100 600 300 100 50 600 300 100 50 L2K UT
HM19A(+35+36)
H20A(+44+71)
H20A(+149+170)
20/20 cocktail
H20A(+44+71)
H20A(+149+170)
19/20/20 cocktail
HM19A(+35+36)
H20A(+44+71)
H20A(+149+170)

FIGURE 10



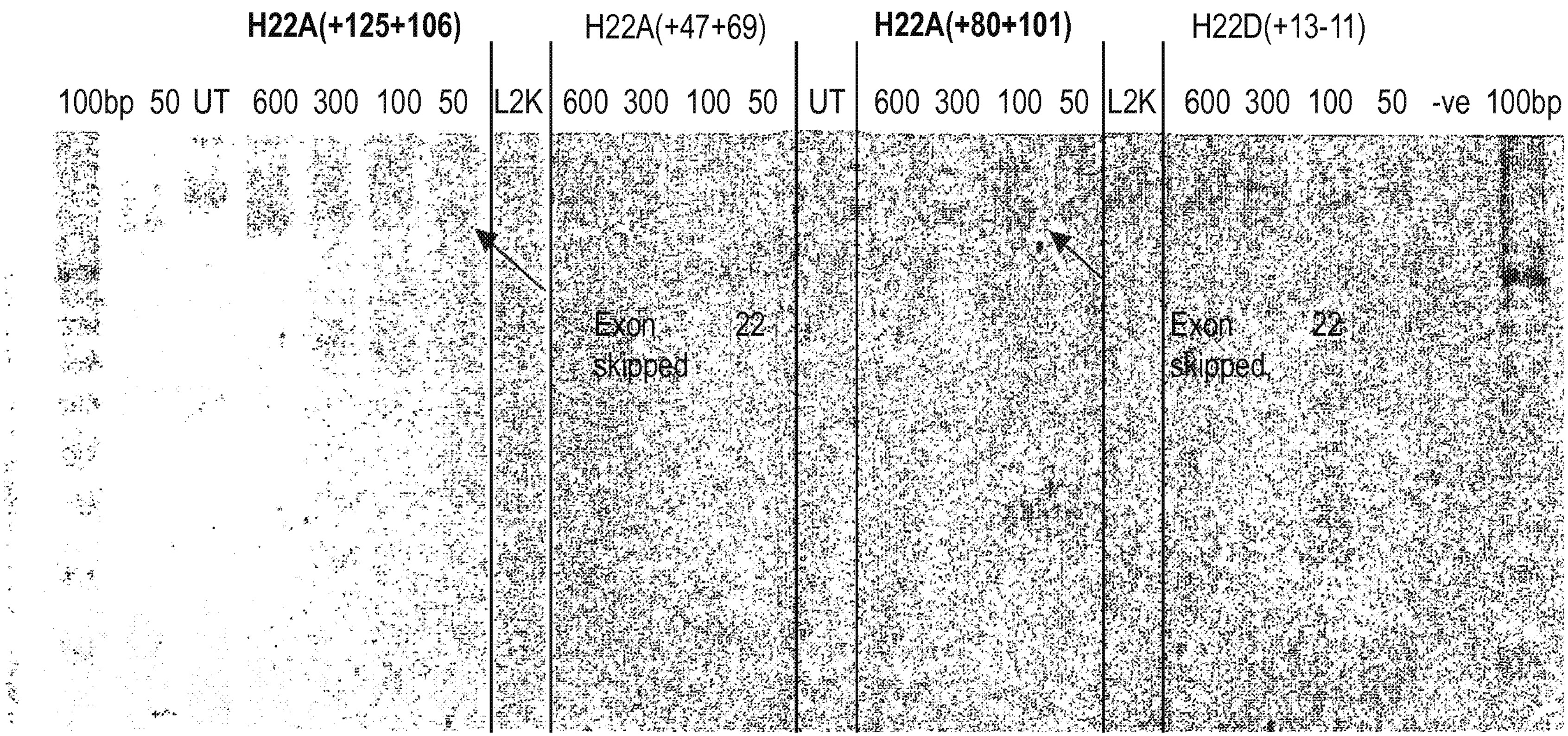
Weasel19/20/20
H19A(+35+53)-aa-
H20A(+44+63)-aa-
H20A(+149+168)

Weasel19/20
H19A(+35+53)-
aa-
H20A(+44+63)

Weasel19/20
H19A(+35+53)-
aa-
H20A(+149+168)

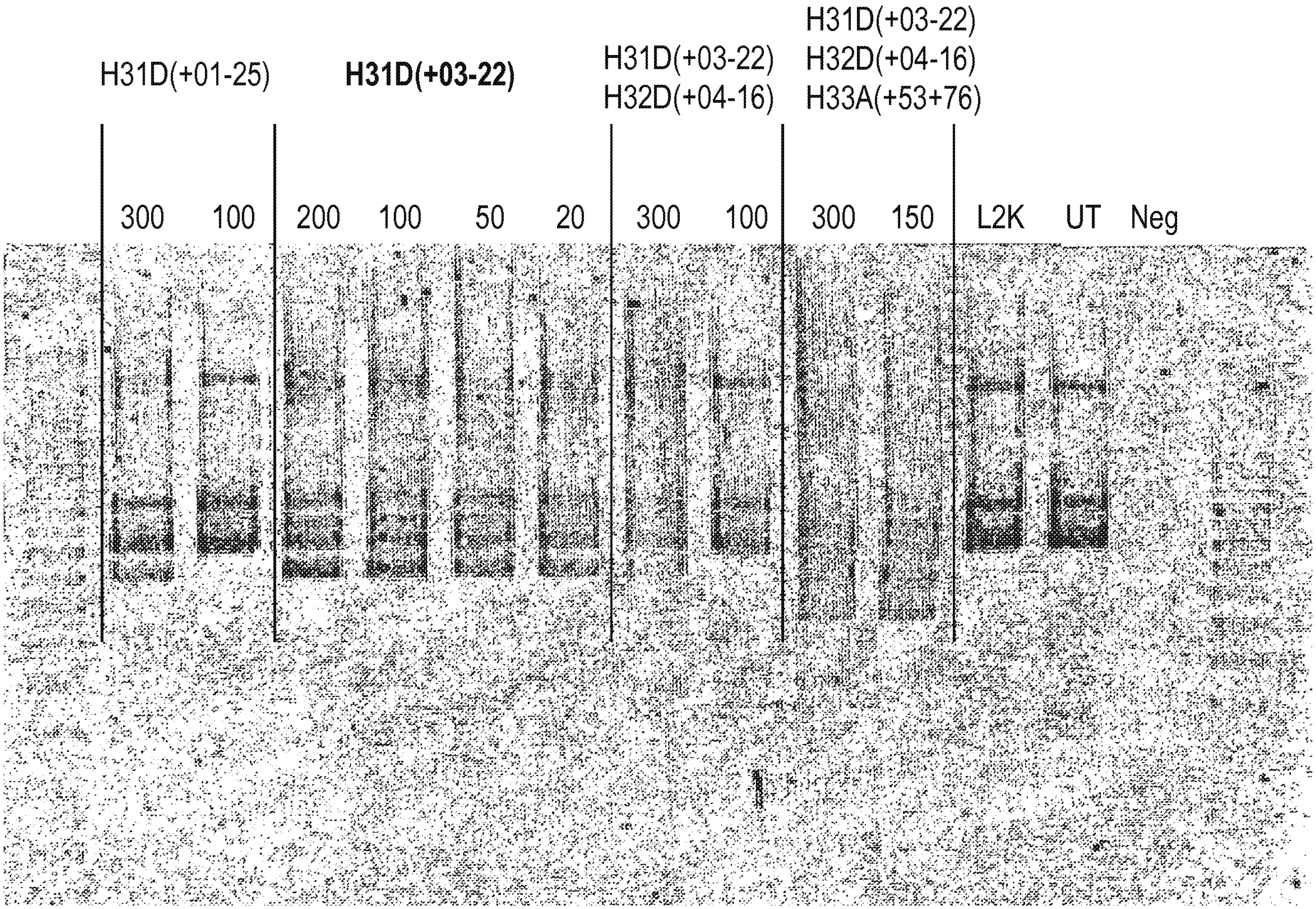
19/20/20 cocktail
HM19A(+35+36)
H20A(+44+71)
H20A(+149+170)

FIGURE 11



12/22

FIGURE 12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H31D(+03-22)
H31D(+03-22)
H32D(+04-16)
H31D(+03-22)
H32D(+04-16)
H33A(+53+76)
300
100
200
100
50
20
300
100
300
150
L2K
UT
Neg

FIGURE 13

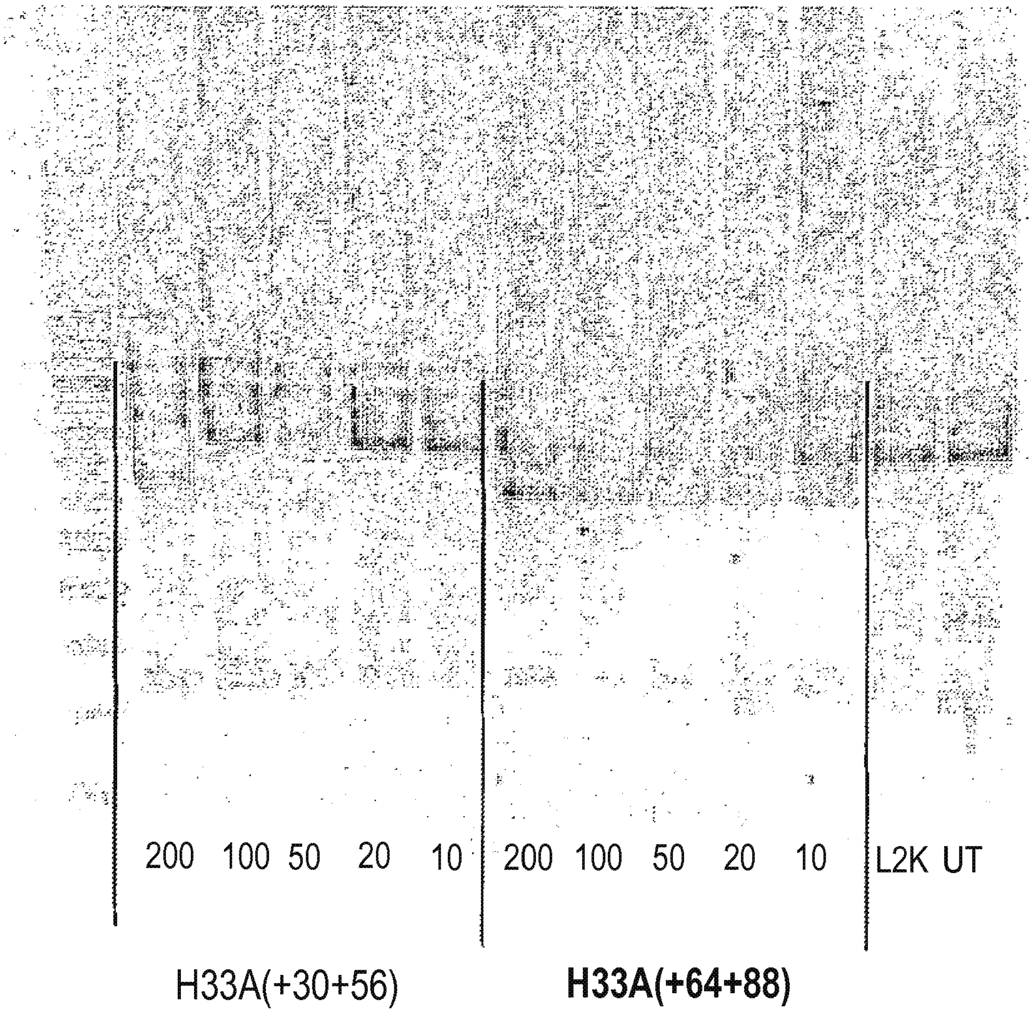
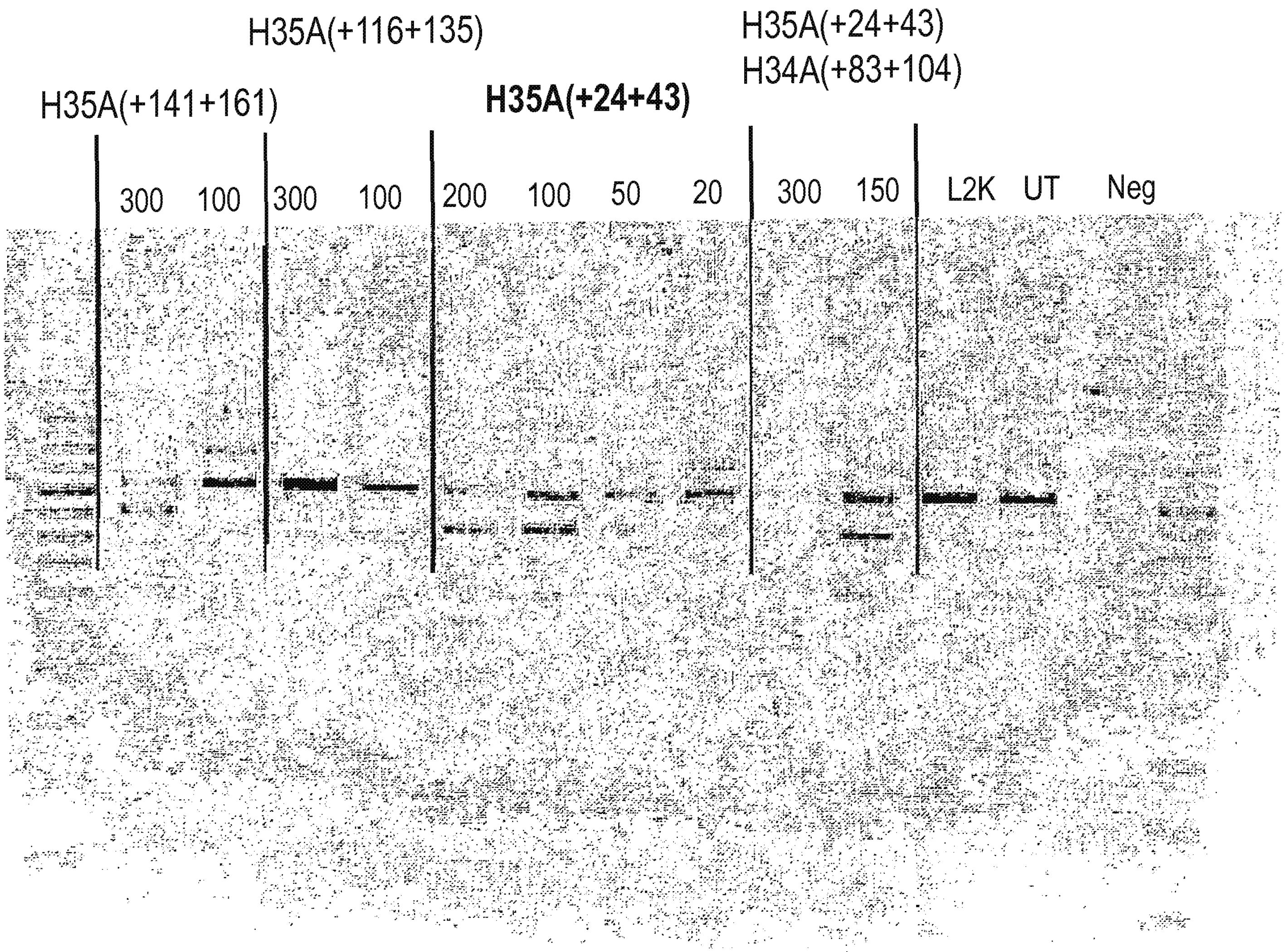


FIGURE 14



H35A(+116+135)
H35A(+141+161)
H35A(+24+43)
H35A(+24+43)
H34A(+83+104)
300
100
300
100
200
100
50
20
300
150
L2K
UT
Neg

FIGURE 15

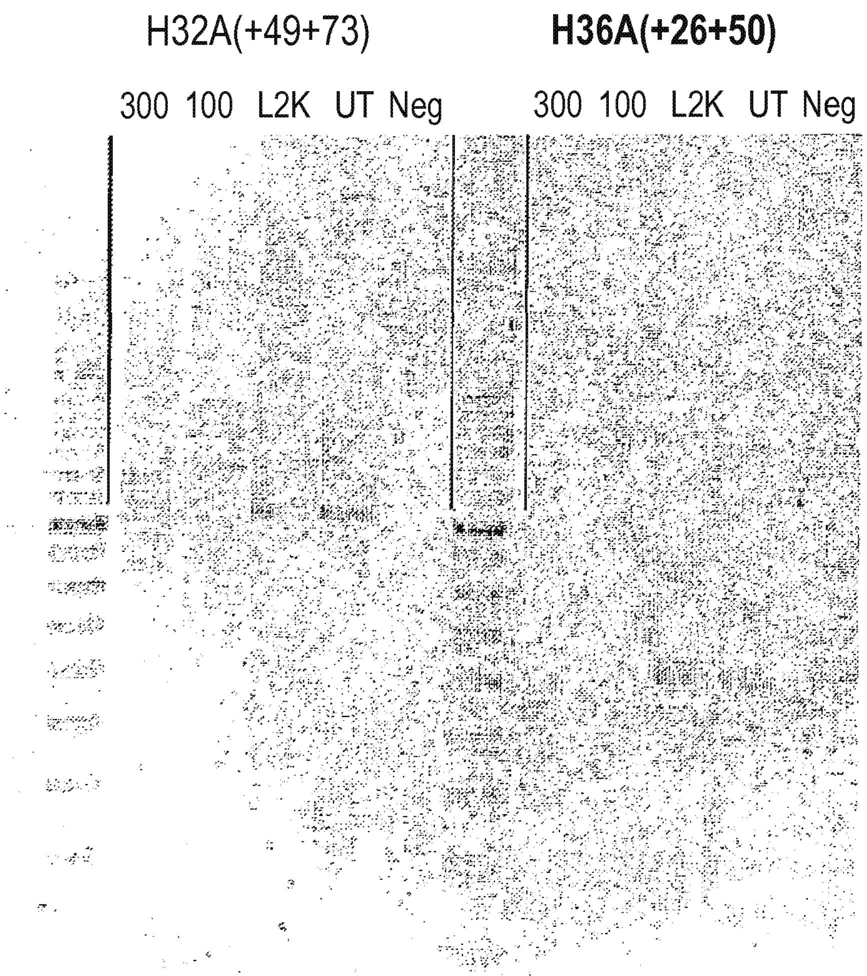


FIGURE 16

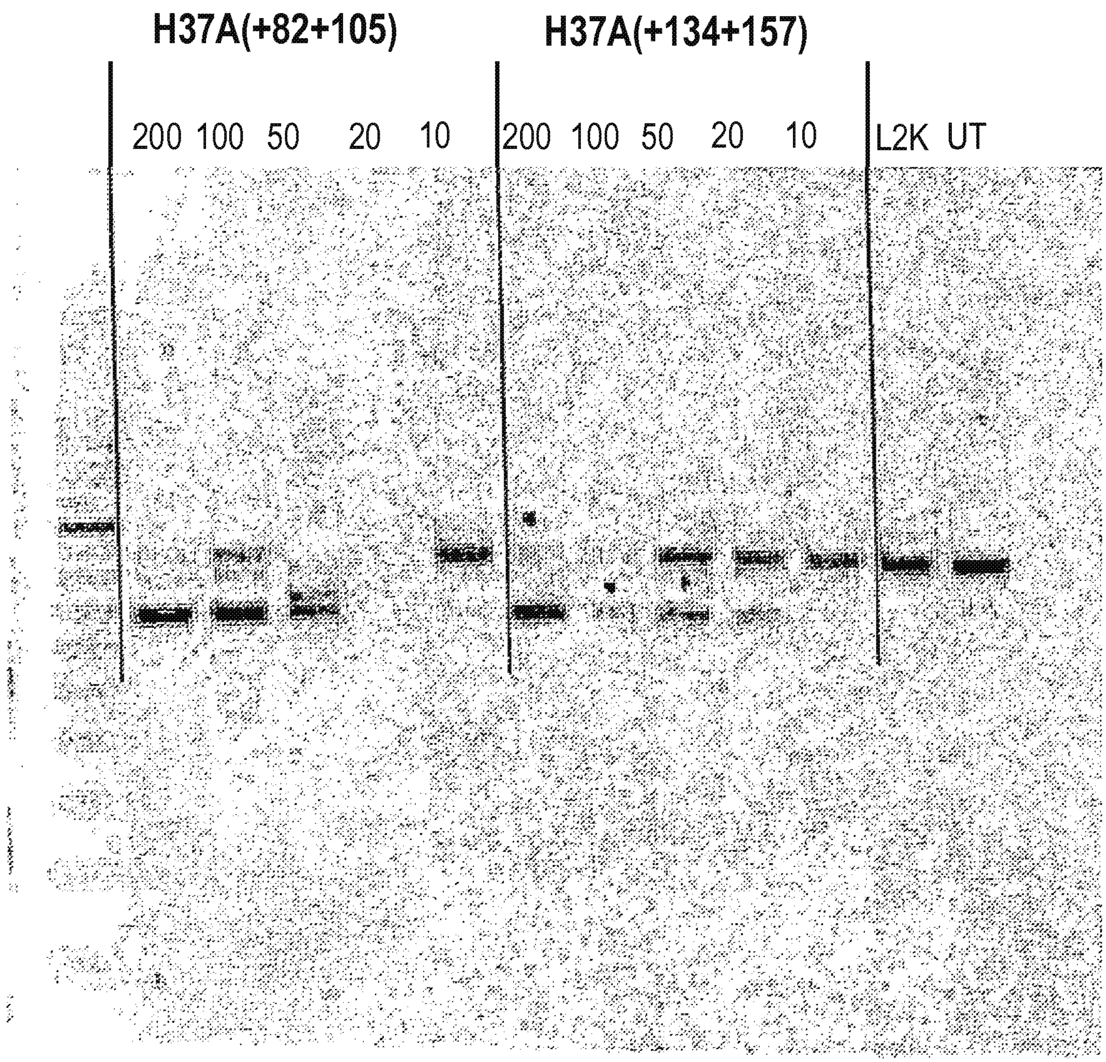


FIGURE 17

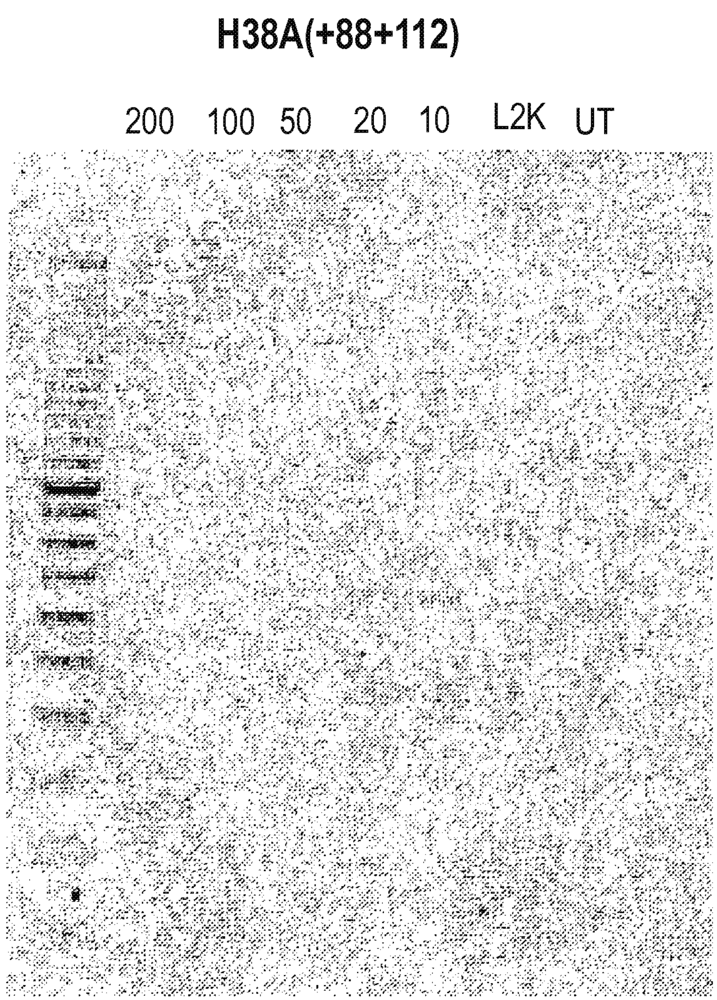


FIGURE 18

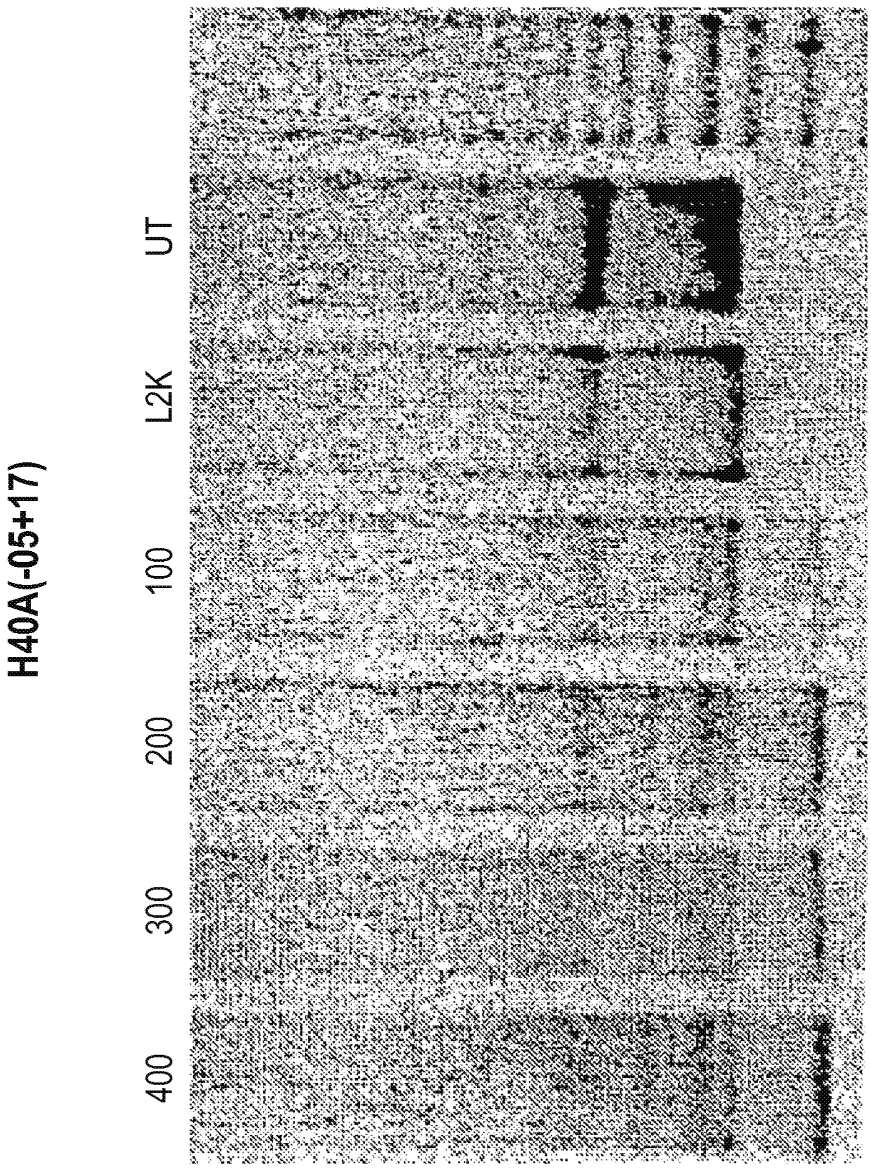


FIGURE 19

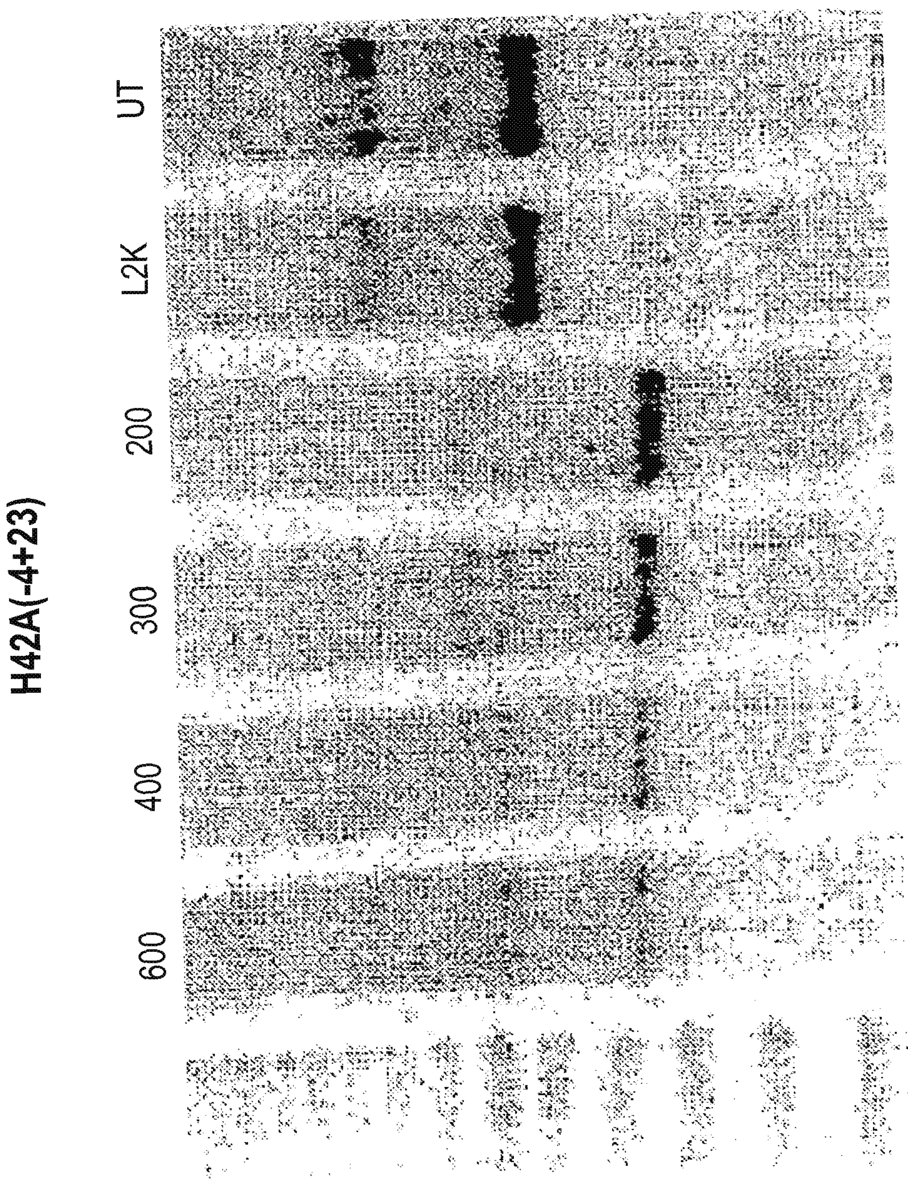


FIGURE 20

H46A(+86+115)

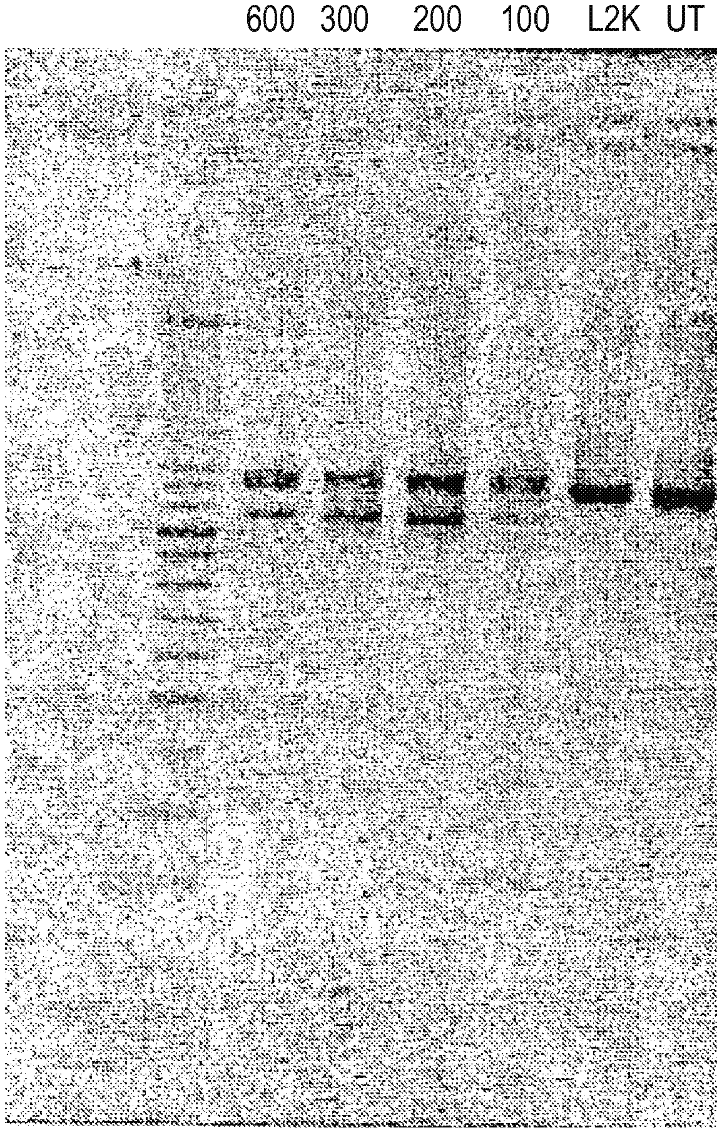
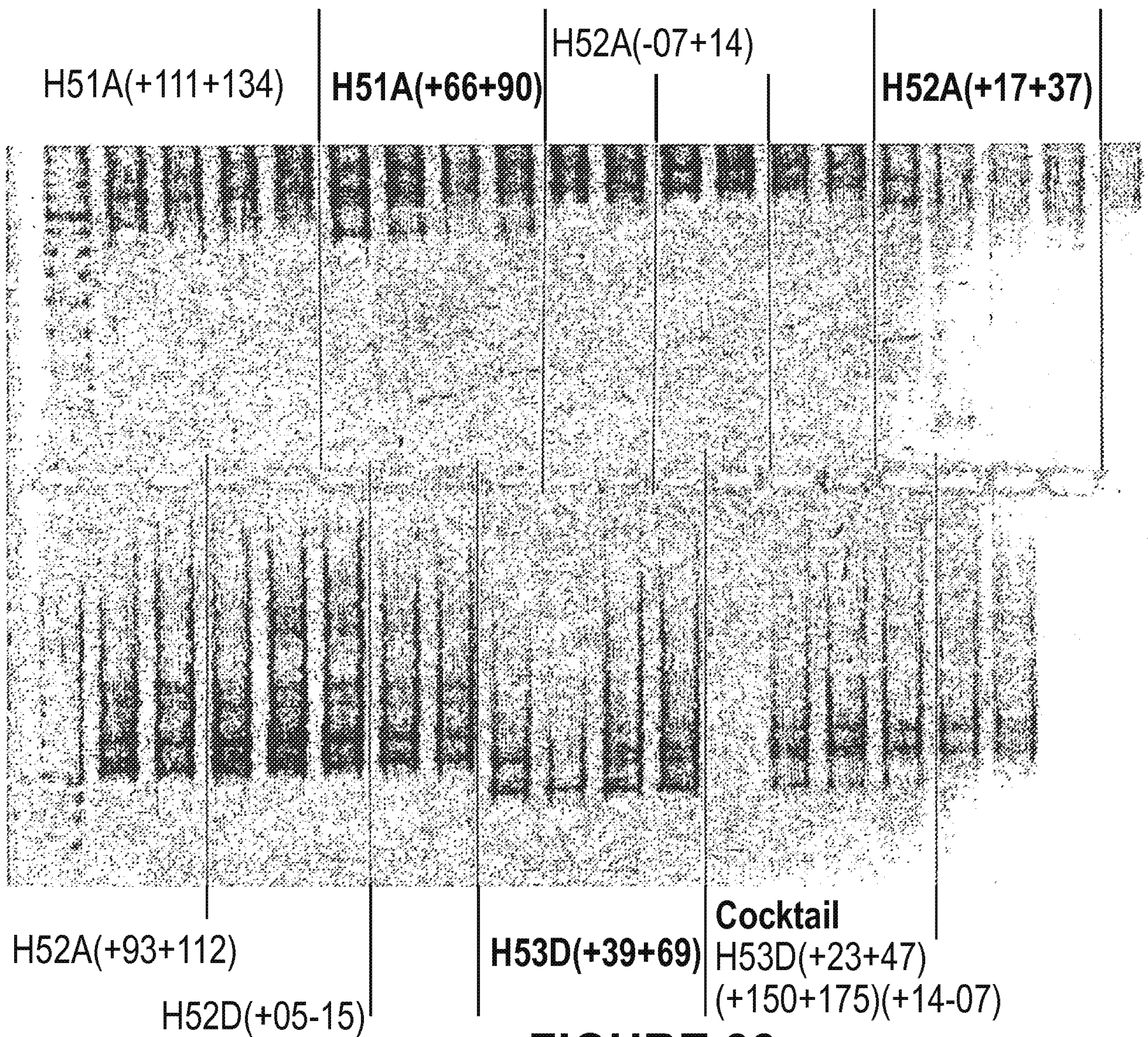


FIGURE 21



H51A(+111+134)
H51A(+66+90)
H52A(-07+14)
H52A(+17+37)
H52A(+93+112)
H52D(+05-15)
H53D(+39+69)
Cocktail
H53D(+23+47)
(+150+175)(+14-07)

FIGURE 22

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AVN-008CN13
	Application Number	

Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

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Legal Name

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Address 2			
City	Applecross	State/Province	
Postal Code	6153	Country	AU

Inventor 2 Remove
Legal Name

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Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Bayswater	Country of Residence	AU

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Address 2			
City	Bayswater	State/Province	
Postal Code	6053	Country	AU

Inventor 3 Remove
Legal Name

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AVN-008CN13
	Application Number	
Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Graham		McClorey	

Residence Information (Select One) ◯ US Residency ◉ Non US Residency ◯ Active US Military Service

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Mailing Address of Inventor:

Address 1	8 Digwood Close		
Address 2			
City	Bayswater	**State/Province**	
Postal Code	6053	**Country**	AU

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	00959
Email Address	ipboston.docketing@nelsonmullins.com

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Application Information:

Title of the Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF		
Attorney Docket Number	AVN-008CN13	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	22	**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AVN-008CN13
	Application Number	
Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	(●) Customer Number	( ) US Patent Practitioner	( ) Limited Recognition (37 CFR 11.9)
Customer Number	00959		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13168857	2011-06-24

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13168857	Continuation of	12/837539	2010-07-15	8232384	2012-07-31

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
12837359	Continuation of	11570691	2008-01-15	7807816B	2010-10-05

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
11570691	a 371 of international	PCTAU2005000943	2005-06-28

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

			Remove
Application Number	Country i	Filing Date (YYYY-MM-DD)	Priority Claimed
2004903474	AU	2004-06-28	(●) Yes ( ) No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AVN-008CN13
	Application Number	
Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Remove

◉ Assignee	○ Legal Representative under 35 U.S.C. 117
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Assignee is an Organization check here. ☒

Organization Name	The University of Western Australia

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AVN-008CN13
	Application Number	

Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

Mailing Address Information:

Address 1	35 Stirling Highway		
Address 2			
City	Crawley	**State/Province**	
Country i	AU	Postal Code	
Phone Number	6009	Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/Amy E. Mandragouras, Esq./			Date (YYYY-MM-DD)	2013-01-14
First Name	Amy	Last Name	Mandragouras	Registration Number	36207

Additional Signature may be generated within this form by selecting the Add button. Add

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: January 14, 2013
Electronic Signature for Amy E. Mandragouras, Esq.: /Amy E. Mandragouras, Esq./

Docket No.: AVN-008CN13
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Donald Wilton *et al.*

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: Concurrently Herewith

Art Unit: 1635

For: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

Examiner: K. Chong

STATEMENT PURSUANT TO 37 CFR 1.821

MS Sequence
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

Submitted herewith in connection with the above-referenced patent application and in full compliance with 37 C.F.R. §§1.821-1.825 is a computer readable copy and paper copy of the Sequence Listing (filed together as a .txt file via the United States Patent Office's Electronic Filing System).

I hereby state that I have reviewed the paper copy of the Sequence Listing, as required by 37 CFR 1.821(c), and have reviewed the computer readable form of the Sequence Listing, as required by 37 CFR 1.821(e), and that the content of the paper and computer readable copies for the above-referenced Patent application are the same as required by 37 CFR 1.821(f)

(note that these documents are submitted as one electronic file). No new matter has been added to the Sequence Listing.

Dated: January 14, 2013

Respectfully submitted,

Electronic signature: /Amy E. Mandragouras, Esq./
Amy E. Mandragouras, Esq.
Registration No.: 36,207
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(800) 237-2000
(617) 742-4214 (Fax)
Attorney/Agent For Applicant

Electronic Acknowledgement Receipt

EFS ID:	14696571
Application Number:	13741150
International Application Number:	
Confirmation Number:	3931
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald Wilton
Customer Number:	959
Filer:	Amy E. Mandragouras/Joanne Connors
Filer Authorized By:	Amy E. Mandragouras
Attorney Docket Number:	AVN-008CN13
Receipt Date:	14-JAN-2013
Filing Date:	
Time Stamp:	18:29:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Specification	Application.pdf	285513 a96ab0a40e71c96aa8ba15baf09e04048b7f59be	no	68

Warnings:

Information:

2	Drawings-only black and white line drawings	Drawings.pdf	8758953 310845a0c8fceccf6aff540a5bb9a332670170b0	no	22
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3	Application Data Sheet	ADS.pdf	1064513 2d0074ff7726b97d4f6e1da12cb5ef6036270ab9	no	6
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4	CRF Statement Paper and CRF are the same	Statement.pdf	27984 a9b93d38d042651009be98b8f8e739519b63db11	no	2
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 13741150 Document Date: 01/14/2013

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Sequence Listing

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

To access the documents in the SCORE database, refer to instructions developed by SIRA.

At the time of document entry (noted above):

- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://es/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

Form Revision Date: February 8, 2006

DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 13741150 Document Date: 01/14/2013

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Drawings – Other than Black and White Line Drawings

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

To access the documents in the SCORE database, refer to instructions developed by SIRA.

At the time of document entry (noted above):
- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://es/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

Form Revision Date: February 8, 2006

==

Sequence Listing was accepted.

See attached Validation Report.

If you need help call the Patent Electronic Business Center at (866) 217-9197 (toll free).

Reviewer: markspencer

Timestamp: [year=2013; month=1; day=25; hr=13; min=37; sec=41; ms=221;]

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Validated By CRFValidator v 1.0.4

Application No: 13741150 Version No: 1.0

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Finished: 2013-01-14 18:30:34.054
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Total Errors: 1
No. of SeqIDs Defined: 214
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Total Warnings: 212

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SEQUENCE LISTING

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FLETCHER, SUE
MCCLOREY, GRAHAM

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OF USE THEREOF

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Human 2'-O-methyl phosphorothioate antisense
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Human 2'-O-methyl phosphorothioate antisense
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PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [ ] The attached application, or
- [x] United States application or PCT international application number 13/741,150 filed on 01/14/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Stephen Donald WILTON   Date (Optional): 26/03/13

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 13/741,150 filed on 01/14/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Sue FLETCHER Date (Optional): 26/03/2013

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 13/741,150 filed on 01/14/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Graham MCCLOREY Date (Optional): 26-03-13

Signature: Graham McClorey

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/22 (03-13)
Approved for use through 03/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) AVN-008CN13
Application Number 13/741,150-Conf. #3931	Filed January 14, 2013
For ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	
Art Unit N/A	Examiner Not Yet Assigned

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☒	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$ 300.00
☐	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3000	$1,500	$750	$

☒ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 12-0080 .

☒ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☒ attorney or agent of record. Registration Number 36,207 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number ______ .

/Amy E. Mandragouras, Esq./	June 7, 2013
Signature	Date
Amy E. Mandragouras, Esq.	(617) 202-4626
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: June 7, 2013 Signature: /Amy E. Mandragouras, Esq./ (Amy E. Mandragouras, Esq.)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: June 7, 2013 Signature: /Amy E. Mandragouras, Esq./
(Amy E. Mandragouras, Esq.)

Docket No.: AVN-008CN13
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Donald Wilton *et al.*

Application No.: 13/741,150 Confirmation No.: 3931

Filed: January 14, 2013 Art Unit: N/A

For: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

Examiner: Not Yet Assigned

MS Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION

Dear Madam:

In response to the Notice to File Missing Parts of Application – Filing Date Granted mailed February 7, 2013, Applicant respectfully submits the inventor Declarations, the Filing Fee for the Application, a Petition for Two-Month Extension of Time, and a Preliminary Amendment. An Information Disclosure Statement, and an Information Disclosure Citation (PTO SB/08) are also being filed herewith.

Please charge our Deposit Account No. 12-0080 in the amount of $1,100.00 covering the fees set forth in 37 C.F.R. § 1.16(f), 1.16(a)(1), 1.16(k), and 1.16(o). The Director is hereby

authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AVN-008CN13.

Dated: June 7, 2013

Respectfully submitted,

By /Amy E. Mandragouras, Esq./
Amy E. Mandragouras, Esq.
Registration No.: 36,207
NELSON MULLINS RILEY &
SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(800) 237-2000
(617) 742-4214 (Fax)
Attorney/Agent For Applicant

Electronic Patent Application Fee Transmittal

Application Number:	13741150
Filing Date:	14-Jan-2013
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Filer:	Amy E. Mandragouras
Attorney Docket Number:	AVN-008CN13

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	2051	1	70	70
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	2252	1	300	300
Miscellaneous:				
		Total in USD ($)		**1100**

Electronic Acknowledgement Receipt

EFS ID:	15975975
Application Number:	13741150
International Application Number:	
Confirmation Number:	3931
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	959
Filer:	Amy E. Mandragouras
Filer Authorized By:	
Attorney Docket Number:	AVN-008CN13
Receipt Date:	07-JUN-2013
Filing Date:	14-JAN-2013
Time Stamp:	17:00:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1100
RAM confirmation Number	4178
Deposit Account	120080
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	Information_Disclosure_Statement.pdf	37657 a771ec4c97ec49077db94aed8e5f29b89b1f45a4	no	5
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Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	SB08-1.PDF	619607 f9effd9213ef863902dce587041529f3897527bc	no	18
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	SB08-2.PDF	614108 295bdc5e3e5893f7858db04a4e326d26e6778ad9	no	6
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
4	Other Reference-Patent/App/Search documents	US_OAs_11-570691.PDF	536346 87c7e321cf8ff9abc1986adbe17a247b5ca97138	no	15
Warnings:					
Information:					
5	Other Reference-Patent/App/Search documents	US_OAs_12-837356.PDF	591007 5d17d9ea109e101617eef44f8d990e93dc8c47a5	no	17
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Information:					
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23	Foreign Reference	EP2135948.PDF	7888542 415b6a133f4770967b4e59642b6913dfb21794ac	no	194
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51	Non Patent Literature	Cirak-Exon.PDF	4443624 be1a8fb8f13bb14a33c836328c80f25baf0ad476	no	21
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52	Non Patent Literature	Dominski-Identification.PDF	530758 e869efaadfa643b4d621079811af2472edb80035	no	10
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53	Non Patent Literature	Dominski-Restoration.PDF	1511439 7fb375c69fc50371b9944b86284a84bf1b0c0b23	no	5
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54	Non Patent Literature	Fall-Induction.PDF	507424 36db540994f83c4e9ee3e715673409f402fcdcb8	no	12
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56	Oath or Declaration filed	Declarations.pdf	223431 92fddf63961d77c1077250f989a10cfc34fed54d	no	3
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59	Fee Worksheet (SB06)	fee-info.pdf	38772 f1ffe028c6245a6049e602db401803aade43e154	no	2
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

EXHIBITS 18-22 REDACTED IN THEIR ENTIRETY